A STUDY OF THE EFFECT OF HIGH PRESSURE ON THE [2 + 2] CYCLOADDITION REACTIONS OF DIFLUOROALLENE

BY

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Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

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The [2 + 2] cycloaddition of difluoroallene proceeds with initial bond formation occurring at C_2, forming an allyl stabilized diradical. Cyclization of the diradical is able to occur with either C_1 or C_3 to form two regioisomers of substituted methylene cyclobutane. A 1,2 disubstituted olefin can undergo cyclization with varying degrees of stereochemical scrambling. The cycloaddition of difluoroallene and Z-ß-deuteriostyrene yields two products, 4-deuterio-2,2-difluoro-3-phenyl-1-methylenecyclobutane and 2-deuterio-3-phenyl-1-(difluoromethylene)cyclobutane, with different degrees of stereochemical retention.

In order to explain the different stereoselectivities two kinetically distinct intermediates are required. A mechanism has been proposed which accounts for the observed stereoselectivities.

This mechanism consists of the formation of an initial high energy intermediate which will undergo cyclization with a low degree of regioselectivity but a high degree of stereoselectivity. Alternatively this initial intermediate can undergo a conformational conversion to a less sterically constrained, lower energy intermediate, which will undergo cyclization with higher regioselectivity and lower stereoselectivity.

These two pathways were predicted to have different volumes of activation. Because $\partial \ln k/\partial P = -\Delta V^{\neq}/RT$, high pressure was predicted to alter the partitioning between paths. The regio- and stereochemistries of products changed dramatically with pressure. The imposition of arbitrary but reasonable path stereoselectivities allowed the fraction of product formed from each path to be calculated. The difference in volume of activation between paths was calculated to be equal to 3.6 cm^3/mol.

Thermodynamic stabilities have historically been used to account for radical reaction selectivities. Steric considerations have traditionally been used to explain high pressure reaction outcomes. This study has investigated diradical reactions occurring at high pressures. Thermodynamics predicts the addition of an α-methyl substituent on styrene should result in an increase in product regioselectivity. Steric considerations predict the addition of a methyl group on styrene will decrease the regioselectivity. Styrene was found to be more regioselective than methylstyrene.

Acrylonitrile was predicted by both thermodynamic and steric arguments to have less regioselectivity than α-methylacrylonitrile.

Steric arguments aptly explain the abnormally low regioselectivity of acrylonitrile.

The observed results strongly support the proposed mechanism and steric control of path partitioning.

CHAPTER ONE
THE [2 + 2] CYCLOADDITION REACTION

Background

The common [2 + 2] cycloaddition of two olefins to form a cyclobutane ring has received considerable mechanistic interest over the years.[1] The theoretically possible modes of reaction are either a one step concerted mechanism or a stepwise mechanism. The stepwise mechanism can proceed with either diradical or dipolar intermediates. Early scientists (1947) proposed the dimerization of tetrafluoroethylene as proceeding through a diradical.[2] Since that time theoretical and experimental arguments have been used to support both concerted and stepwise mechanisms.

The absolute determination of how a reaction proceeds is very difficult to accomplish, and the mechanisms of cycloaddition reactions have proved to be among the most formidable to discern. The problem of distinguishing between a stepwise or a concerted mechanism is a common difficulty and has been intimately associated with the relatively new radical-cation addition mechanistic debate[3] as well as in the case of the time-honored Diels-Alder reaction.[4] It is generally considered impossible to prove the validity of a specific mechanism. The support in favor of a specific mechanism comes instead from disproving potentially viable alternatives and the use of Occam's razor.[5]

It was not until thorough stereochemical studies were performed[6] by Bartlett and Schueller, that the stepwise addition process of the [2 + 2] cycloaddition reaction was firmly established. The thermal cycloaddition reaction of dichlorodifluoroethylene and E,E-2,4-hexadiene was carried out and the stereochemistries of all resulting products were analyzed.

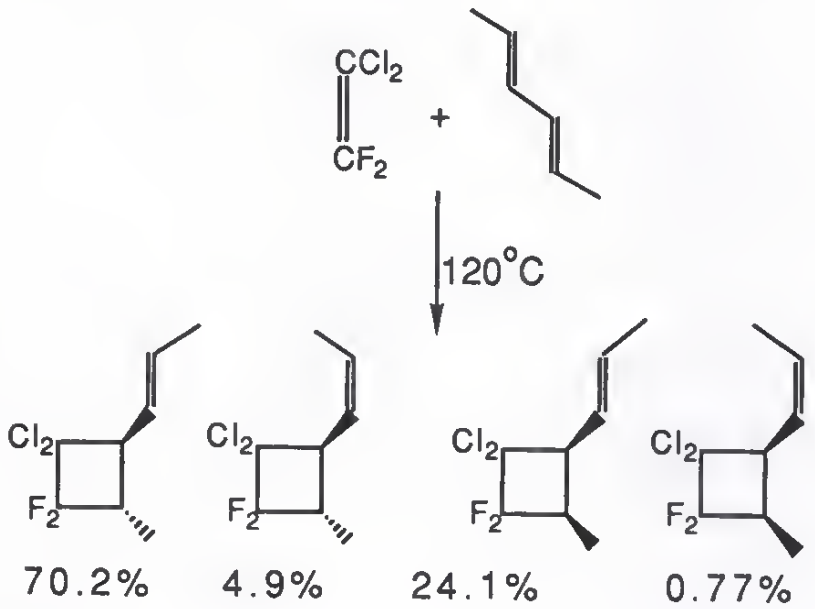


Figure 1. Product Stereochemistries of E,E-Hexadiene and Dichlorodifluoroethylene.

A scrambling of the initial E reactant conformation occurred. An appreciable amount of the less thermodynamically stable Z conformation was found in the product mixture. This strongly suggests the existence of a stepwise diradical addition mechanism.

Additional strong support for the diradical process was brought about by the monumental theoretical work by Woodward and Hoffman.[7] Woodward and Hoffman proposed a set of rules which

assess the viability of concerted reactions. The fundamental criterion whereby a concerted process is allowed to occur is if the orbital symmetry characteristics of reactants and products are conserved over the reaction course. The reaction system under scrutiny is first simplified, only the orbitals undergoing bond breaking or bond making are taken into account. Orbitals not directly involved in bond alterations maintain a relatively constant energy profile, and hence do not yield much insight into the reaction dynamics. All orbitals have an associated phase. Bond formation can be viewed as resulting from a constructive overlap of orbitals with matching phases. The symmetry characteristics of the reactants and products are initially examined with respect to two perpendicular reflecting planes in order to assess the phase orientation in the pertinent reacting orbitals (Figure 2).

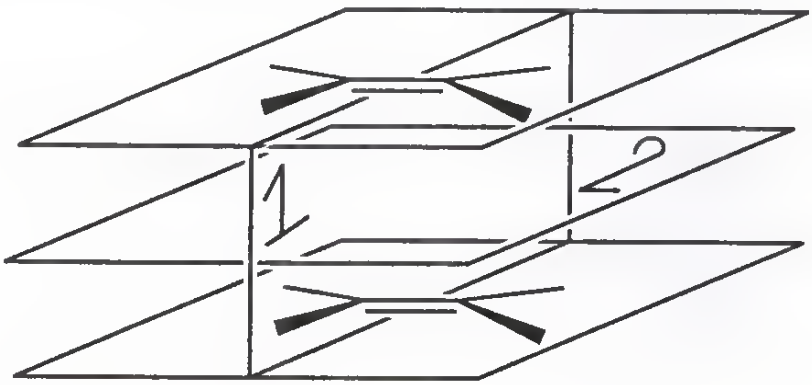


Figure 2. The Symmetry Planes with which Orbital Symmetry has been Examined.

The compatibility of symmetry of the starting materials with the products gives a basis upon which the viability of a process can be assessed. For the [2 + 2] reaction the fundamental components of interest are ethylene and cyclobutane. The symmetry of all energy levels of both ethylene and cyclobutane are determined and recorded in a two letter code, the first letter of which refers to the symmetry of the molecule in respect to the first plane, the second to the second, S indicating symmetrical, A asymmetrical (Figure 3). In order for a cyclization to be allowed, a pairing must exist between all of the symmetry characteristics of the starting materials with the symmetry characteristics of the products without mixing ground state with excited state energy levels (filled with nonfilled).

Inspection of Figure 3 reveals that in order to adequately pair all of the symmetry elements between reactant and product molecular orbitals it is necessary to mix ground state orbitals with those in excited states (π SA with σ SA, and π AS with σ AS). One filled energy level of ethylene must be paired with a non-filled energy level of cyclobutane, as well as a non-filled ethylene energy level must be paired with a filled level of cyclobutane. Thus while maintaining symmetry, two ground state ethylene molecules cannot combine to form a ground state cyclobutane. This crossing between filled and non-filled energy levels was strongly stated by Woodward and Hoffman as being accompanied by a very large symmetry-imposed energy barrier. Thus the concerted [2 + 2] cycloaddition

reaction mechanism has been designated as being symmetry-forbidden.

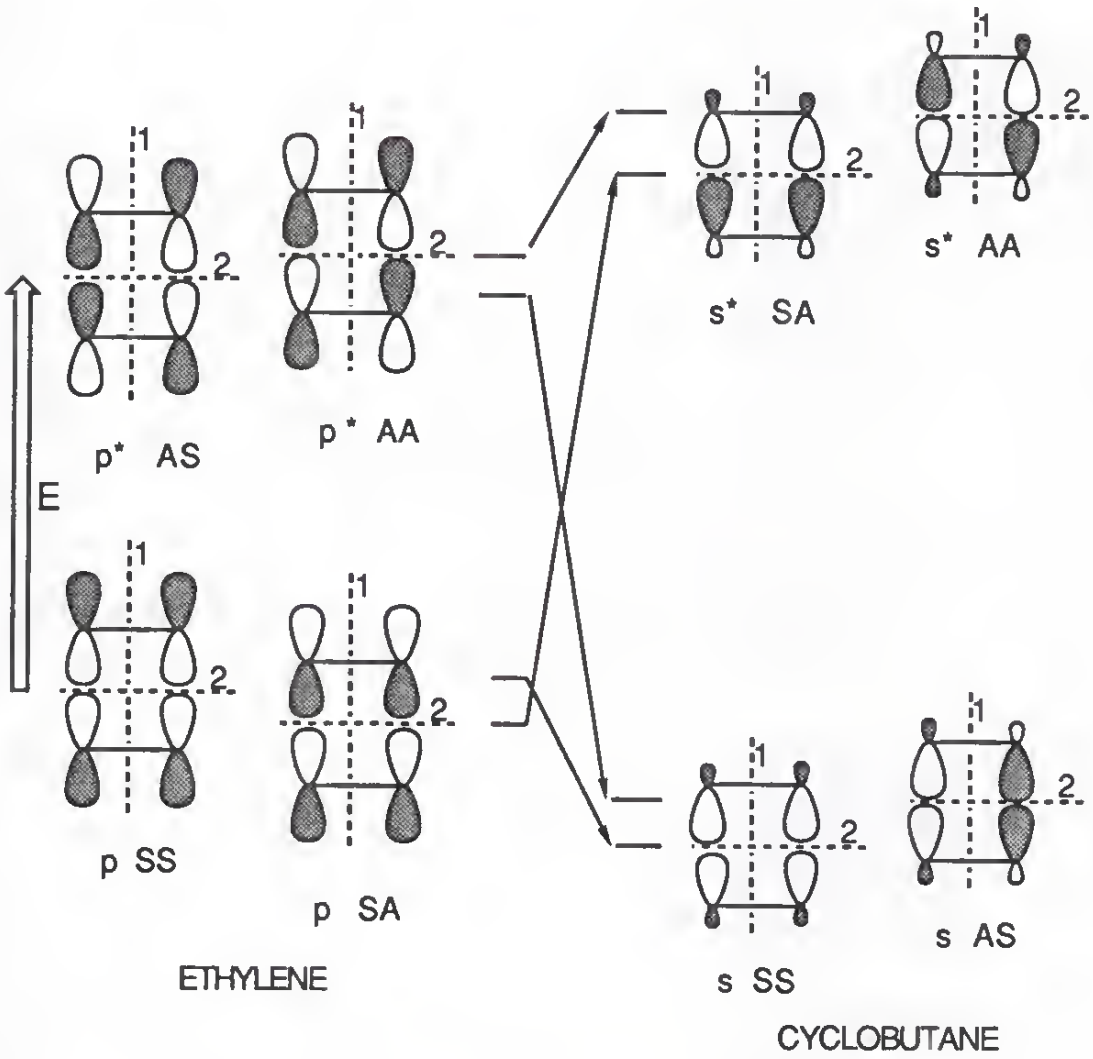


Figure 3. Symmetry Correlation Diagram for the Formation of Cyclobutane from Ethylene.

More recent (1978) experimental support for a stepwise addition was performed by Doering and Guyton[8]. They statistically

analyzed the stereochemical product outcome from the dimerization reaction of pure E-1,2 dideuterioacrylonitrile. The six cyclobutane stereoisomers which were observed, three each of erythro and threo, were a result of zero, one, and two internal bond rotations about the α,β and α',β' bonds. These results prompted this resolute response, "Our findings are inconsistent with a stereorandom process and unsupportive of even a vestige of concerted [$_p2_s$ + $_p2_a$] reaction" (8, p3230).

The preceding strong evidence against a concerted addition still allows for two alternatives: incorporating either a dipolar or a diradical intermediate. While there exists strong evidence supporting a dipolar [2 + 2] reaction mechanism when the reaction is carried out with good charge stabilizing olefins such as enamines, tetracyanoethylene and some Lewis acids.[9] This is not the normal situation with hydrocarbon systems. If a dipolar mechanism were operating, olefin [2 +2] dimerization would be expected to yield products with a head-to-tail orientation of substituents (Figure 4).

The head-to-tail orientation is not present when standard olefins undergo dimerization. Instead, what is observed[10] is a head-to-head orientation. This strongly opposes the existence of a dipolar intermediate. Additionally, the fact that [2 + 2] cycloaddition reactions commonly proceed well in non-polar solvents[11] is another sound argument against an ionic mechanism. Hexane for example, is commonly used as a solvent in performing [2 + 2] cycloaddition reactions.

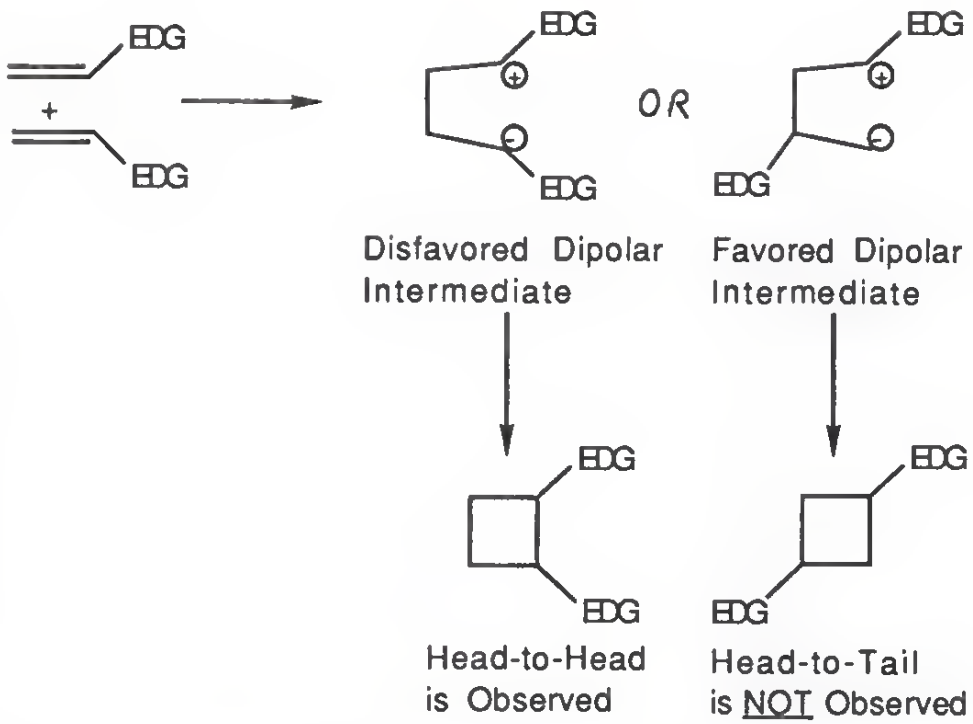


Figure 4. Substituent Orientation Not Consistent with a Dipolar Mechanism of Cycloaddition.

This evidence opposing a dipolar mechanism coupled with the previous evidence against a concerted mechanism leaves one logical alternative; a stepwise diradical mechanism. In fact, the view of a step-wise diradical [2 + 2] cycloaddition is presently so widely accepted that it is the only explanation presented in standard organic texts.[12] Although the basic concept of this mechanism is understood, the precise details remain for the most part unknown.

Mechanism

The diradical [2 + 2] cycloaddition mechanism is generally believed to occur by initial carbon-carbon bond formation (k_1),

generating a 1,4 diradical. This diradical is able to undergo either bond homolysis (k_{-1}) regenerating starting material, or combination of the two radicals (k_2), forming cyclobutane (Figure 5).

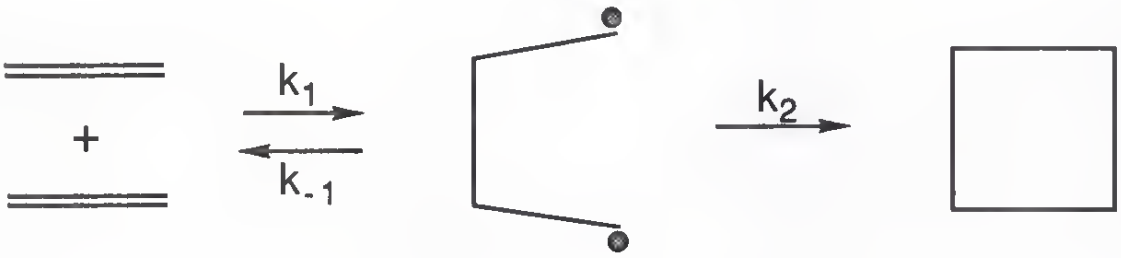


Figure 5. General Diradical Addition Sequence.

The process of going from two stable olefin molecules to a reactive diradical (k_1), has quite a substantial energy of activation. Hence it is not surprising that the [2 +2] cycloaddition is not a general reaction. The cycloaddition reaction does not occur with most alkenes. In fact [2 + 2] cycloadditions only proceed with significantly activated olefins.[13]

The 1,4 diradical intermediate is a highly energetic species and exists in a very shallow energy well. An energy reaction sequence depicting the dimerization of ethylene has been proposed[14] (Figure 5). The energy of activation necessary for the diradical intermediate to return to ethylene (E_{a-1}) has been predicted to be very similar to the energy necessary for the intermediate to go on to cyclobutane (E_{a2}). Hence another reason for the [2 + 2] cycloaddition reaction occurring in such poor yields is that once the diradical

intermediate is formed, the reverse reaction, proceeding back to starting material, is quite competitive with the forward product forming reaction ($E_{a-1} \approx E_{a2}$).

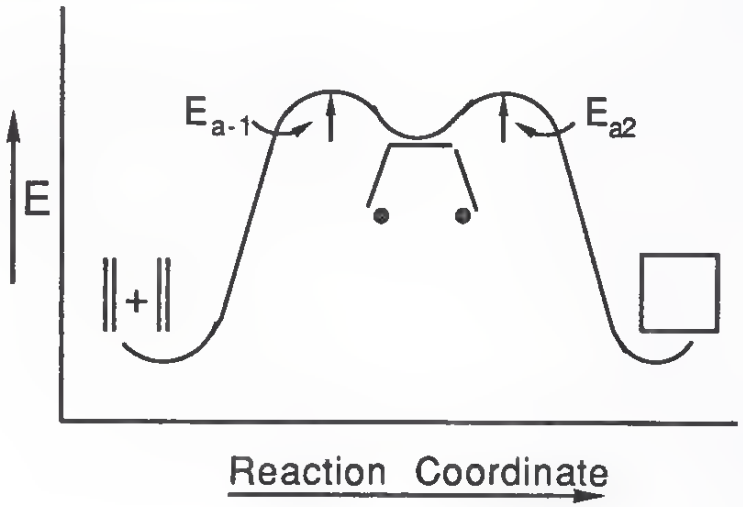


Figure 6. Energy diagram for diradical [2 + 2] addition.

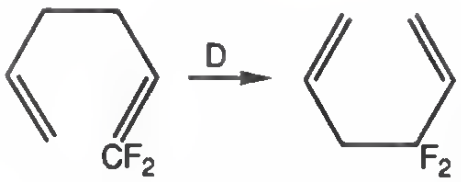
In general, [2 + 2] reactions proceed very slowly if at all. In order to achieve reasonable yields of cyclobutane product, two circumstances must be present. First, the energy of activation necessary for the intermediate to proceed forward through the second transition state (E_{a1}) must be lower than the activation energy to regress backward to the starting material ($E_{a2} < E_{a-1}$). Secondly, the energy of activation necessary for the reacting olefins to reach the initial transition state must be of small enough magnitude to ensure this reaction pathway is reasonably accessible, thereby allowing an appreciable amount of the intermediate to form (lower E_{a1}).

Decreasing E_{a2} in Respect to E_{a-1}

The means whereby E_{a2} can be lowered in respect to E_{a1} can be elucidated by examining the different qualities associated with the two alternative paths available to the intermediate. The fundamental difference in the paths which are available to the intermediate is that the intermediate can either proceed to an sp^3 hybridized strained cyclobutane ring, or to an unstrained sp^2 olefin. Radicals are known to posses a significant amount of sp^2 character.[15] Therefore the intermediate begins with predominate sp^2 character, and is able, by following the reaction coordinate to the left, to achieve true sp^2 hybridization. Alternatively, the intermediate can follow the reaction coordinate to the right and obtain sp^3 character. Hybridization and ring strain are the basic difference between the two paths. If E_{a2} is to be lowered with respect to E_{a-1}, reactants should be chosen which 1)prefer an sp^3 rather than an sp^2 hybridization and 2)do not possess such steric constraints as to impede cyclobutane formation.

Hybridization considerations

In order to decrease E_{a2} with respect to E_{a-1}, an olefin can be utilized which has substituents that prefer to exist in a sp^3 geometry A dramatic thermodynamic preference of sp^3 over sp^2 hybridization can be found in the case of fluorinated olefins. It has been shown that a gem-difluoro group prefers a sp^3 configuration by approximately 5 Kcal/mol.[16]



DH = -5.1 +/- 0.6 K cal/mol

Figure 7. Preference of CF_2 to Exist on a sp^3 Carbon.

This preference has often been explained by the concept of double bond-no bond resonance. Fluorine being a member of the second period, has the potential for excellent orbital overlap with carbon due to the fact that their orbital size is very similar. Fluorine is known[17] to be a good p electron donor, which stems from this select overlap and the ease of fluorine to backbond. Fluorine with the largest Pauling electronegativity (3.98),[18] will also quite readily take on a negative charge. It therefore follows the gem-difluoro substituent should quite readily undergo double bond-no bond resonance.

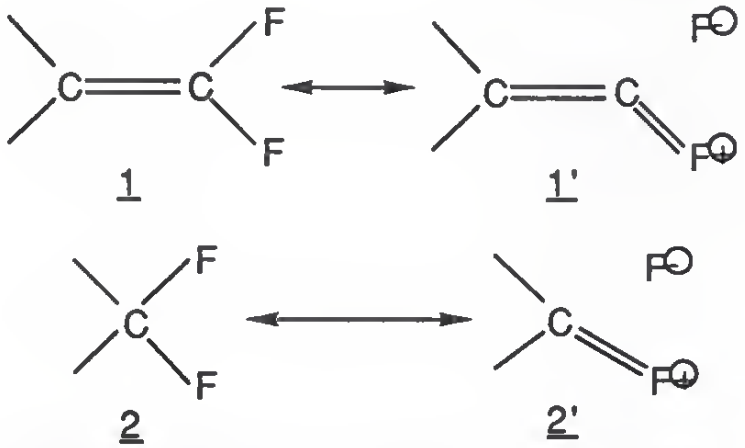


Figure 8. Hyperconjugation of Vinylic and Alkylic Gem-Difluorosubstituents Systems.

The basic changes which occur upon hyperconjugation are the increase in bond order to fluorine, and the cleaving of a carbon fluorine bond. The increase in bond order to fluorine is the same in both the alkyl and the vinyl system. The carbon-fluorine bond which breaks is different in both cases. The alkyl system undergoes an sp^3 bond cleavage, whereas the allyl system undergoes an sp^2 bond breakage. It takes much more energy to break an sp^2 bond than an sp^3 bond. Thus the energies gained by the added bond are similar but the bond cleavage energy are different. The energy lowering brought about by double bond-no bond resonance of an sp^3 center is much greater than that from an sp^2. This resonance contribution of the vinylic system (1') can then be expected to be minimal[18] in relation to the alkyl system (2'). The preference of difluorosubstituted molecules to exist on saturated carbons can then be attributed to the added stability of the alkyl (sp^3) orientation due to the lowering in energy brought about by this resonance stabilization (2'). It is the ease in which this occurs, which satisfactorily explains[19] the thermodynamic preference of gem-difluorine to exist on an sp^3 center.

The process of fluorinating cyclobutanes has actually been shown[20] to stabilize the rings against thermal fragmentation. Perfluorocyclobutane is almost 12 Kcal/mol more stable than the hydrocarbon analog.

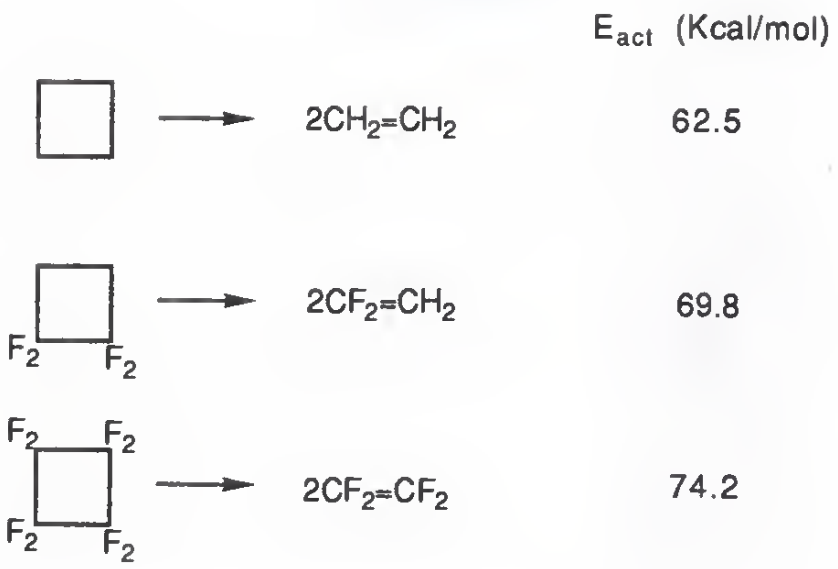


Figure 9. Cyclobutane Thermolysis Energies.

It is evident that fluorination stabilizes a cyclobutane ring. A difluoromethylene would thermodynamically prefer to exist in an sp^3 cyclobutane ring than in an sp^2 olefin, thereby effectively lowering E_{a2} with respect to E_{a-1}.

Another method whereby E_{a2} could be lowered is if an olefin is utilized in which the back reaction, to starting material is disfavored (increased E_{a-1}). Such olefins would consist of systems in which formation of the diradical would bring about a significant decrease in energy. Methylenecyclopropane is such a system. Upon initial [2 + 2] bond formation, the sp^2 hybridized carbon of cyclopropane becomes rehybridized to sp^3. This alteration gives rise to a 12 kcal/mol relief of strain energy.[21] The energy required for the diradical intermediate to return to methylenecyclopropane would

be prohibitively large to allow the reverse, nonproductive reaction to occur. Thus E_{a2} has effectively been lowered in respect to E_{a-1}.

Another analogous system where the reverse reaction is particularly disfavored can be found in the case of allenes. In order for the diradical intermediate to return to starting material an energetic uphill transformation must occur. The lowering in energy which results from allene undergoing a change in hybridization of the center carbon from sp to sp^2 is approximately equal to 11 kcal/mol.[22] This is quite a large energy barrier and therefore almost all of the diradical intermediate formed will proceed to product.

The use of fluorinated olefins, methylenecyclopropanes, and allenes should greatly facilitate the overall yield of the [2 + 2] cycloaddition by the effective lowering E_{a2} with respect to E_{a-1}.

Steric considerations

Unsubstituted ethylene does not undergo [2 + 2] cycloadditions.[12] Proper substituents must be present on the olefin in order to induce the forward reaction to occur, but these groups cannot possess significant steric bulk. If bulky groups are present the cyclization step can be impeded by the steric repulsion of the large substituents. Therefore the substituents chosen should be sterically small in addition to inducing the [2 +2] reaction to proceed.

Fluorinated olefins

The fluorine atom has the smallest VanDerWaals Radius (0.72 Å) of any element with the exception of hydrogen (0.37 Å).[18] The effective volume of fluorine is such that steric hindrance does not play an active role in dictating the behavior[23] of fluorinated compounds. The use of steric arguments in explaining fluorinated system reaction outcome is commonly invalid. Many cases exist where it has been demonstrated that fluorine behaves sterically very similar to hydrogen.

This lack of steric influence has been demonstrated[24] with the [2 + 2] cycloaddition of monofluoroallene with 1,1-dichloro-2,2-difluoroethylene (Figure 10). Formation of the diradical intermediate can occur with the fluorine either pointing into, or away from the bulk of the molecule. The partitioning between alternative orientations is indicative of the steric bulk of the substituent. A very bulky group would be expected to rotate outward almost exclusively, forming predominantly the less sterically hindered intermediate. The relative proportion of this intermediate can be ascertained from the amount of the corresponding product (A). The reaction of fluoroallene and 1,1-dichloro-2,2-difluoroethylene yielded an equal amount of the two products (A to B is 1 to 1). Therefore an equal amount of the two corresponding intermediates were formed, and hence fluorine and hydrogen exerted the same steric influence.

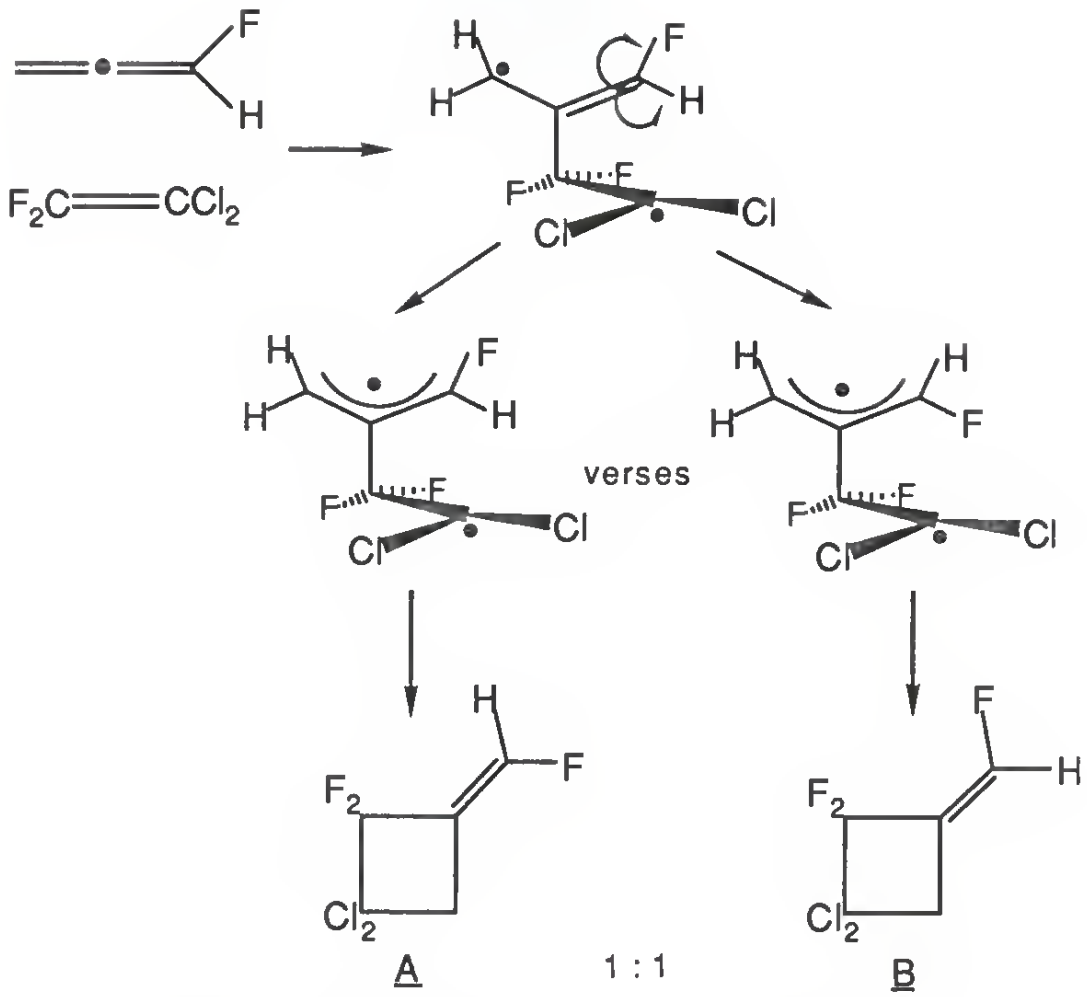


Figure 10. Reaction of Fluoroallene with 1,1-Dichloro-2,2-Difluoroethylene.

Endocyclic fluorinated product was also formed, but was omitted from the above scheme on account of the lack of insight which it imparts into the system. Fluorine commonly exerts the same steric influence as hydrogen.

The fact that fluorine is very small and possesses a distinct thermodynamic thrust to exist in a sp^3 hybridization state makes fluorinated olefins abnormally reactive to [2 + 2] cyclizations.

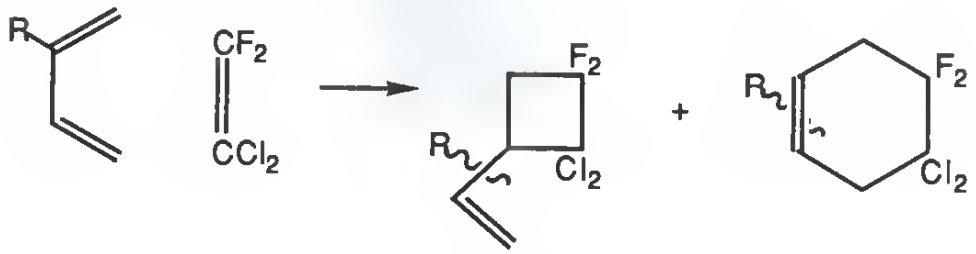
This reactivity has sparked a considerable amount of contention directed toward the possibility of a separate [2 + 2] mechanism operating with fluorinated olefins. For example, the reaction of tetrafluoroethylene and trifluoronitrosomethane, has been proposed,[25] because of an abnormally low Arrhenius pre-exponential factor, to proceed by a concerted mechanism.

More recently (1985) Roberts[26] notes approximately five problems with the stepwise mechanism operating on fluorinated olefins. He then proceeds to present and defend a concerted [$2_s + 2_a$] mechanism of addition for fluorinated olefins.

This is not meant to suggest the existence of a widespread backing of the concerted mechanism, but rather to illustrate the fact that the diradical cycloaddition mechanism has not been thoroughly explored nor is it definitively understood.

The cycloaddition reactions of fluorinated olefins follow some anomalous patterns and have generated a great deal of interest in their behavior, but as of yet, no complete explanations. Some behavior unique to fluorinated olefins includes the fact that when given a choice of reacting with either an identical olefin to undergo dimerization, or with a dissimilar olefin, they prefer to react with a dissimilar olefin. Another facet unique to fluorinated olefins is that they prefer to add in a [2 + 2] fashion even when a symmetry-allowed concerted [2 + 4] pathway is available (illustrated in Table 1). This is exactly opposite to the preferences of all other olefins.

Table 1. Relative Modes of Addition of Difluorodichloroethylene to Substituted Butadienes.



R=	Ratio of 1,2 to 1,4 Addition
H	99 > 1
CH_3	98 : 2
CH_2-CH_2-CH_3	96 : 4
CH-$(CH_3)_2$	84 : 16
C-$(CH_3)_3$	55 : 45
Ph	88 : 12

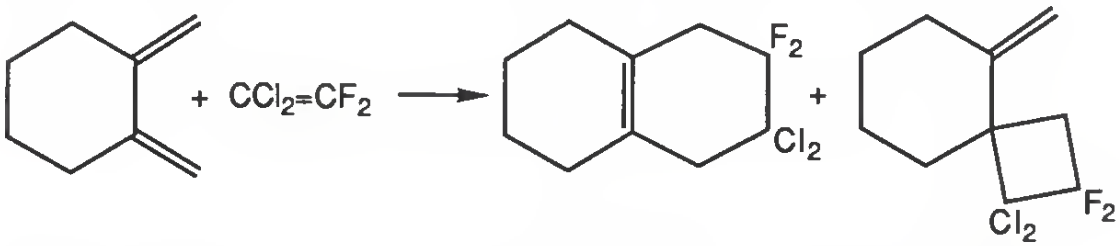
The preference for 1,2 addition has been explained by noting that a butadiene exists primarily in a transoid geometry.[27] In order for a concerted Diels-Alder reaction to take place, the interatomic distance between the terminus of the 1,3 diene and the olefin must be sufficiently close to allow good orbital overlap. The optimum distance between diene terminus can be estimated to be approaching that of the product, 1.54 Å. Steric bulk in the 2 position is known to dissuade the existence of the transoid conformer (Figure 11) due to the interaction between the 2 and 3 position substituents. Table 1 exemplifies the fact that as the steric bulk is increased more 1,4 cycloaddition results. Tert-butyl substituted butadiene yields almost 50% of the [2 + 4] cycloaddition.

[2 + 4] Reaction
Not Allowed

[2 + 4] Reaction
Geometrically Allowed

Figure 11. Preference of Transoid Geometry for Substituted Butadienes.

Substituted 1,3 dienes exist primarily in the transoid form, the olefin is exposed to very little butadiene in the proper conformation necessary for 1,4 addition. The fluorinated olefins, being abnormally reactive, go on and react in a 1,2 manner rather than waiting for the proper cisoid conformation to appear. When fixed cisoid dienes were reacted[27] with 1,1-dichloro-2,2-difluoroethylene a distinct increase in the amount of 1,4 cycloaddition product was obtained, but there still was formed almost 50% of 1,2 addition product.



56% 44%

Figure 12. Relative Orientations of Addition for a Fixed Cisoid Diene.

This preference for [2 + 2] reaction orientation is not well understood.

In summation, the lowering of E_{a2} in respect to E_{a-1} can be accomplished by two means. The first is by utilizing substituents which would rather exist in an sp^3 geometry rather than in an sp^2. The methylenecyclopropane system and gem-difluoromethyl substituted olefins are known for their sp^3 geometrical preference. Secondly, sterically insignificant substituents can be utilized so as to not impede cyclobutane ring formation. This lowering of E_{a2} in respect to E_{a-1} allows cyclization, forming cyclobutane to compete effectively with bond homolysis, returning to starting material.

Fluorinated olefins have substantial advantages in being used in [2 + 2] cycloaddition reactions. The fluorine substituent is very small so no deterring steric factors exist to prohibit cyclization. The gem-difluoromethylene group prefers to exist in a sp^3 geometry and thus a considerable thermodynamic thrust exists toward cyclization.

In addition another approach which induces the [2 + 2] cycloaddition to occur in reasonable yield is the lowering of E_1.

Decreasing E_{a1}

The problem of lowering the value of E_{a1} can be approached in two directions, either by lowering the energy of the diradical intermediate or by raising the reactivity of the starting olefin.

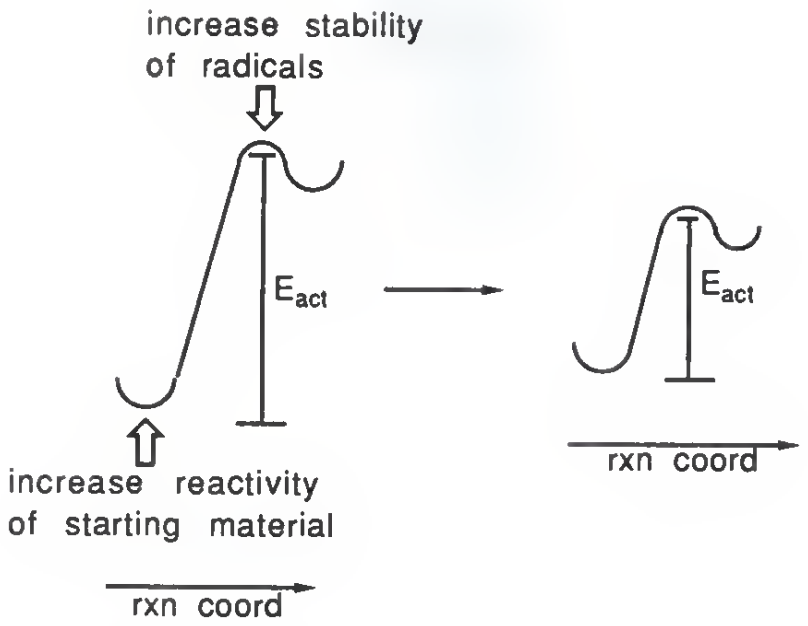


Figure 13. Methods of Lowering the Activation Energy.

Lowering the energy of the diradical

The diradical can be made lower in energy by the introduction of radical stabilizing substituents onto the olefin. Common radical stabilizing substituents include groups which stabilize by electron donation, and by resonance stabilization.[28] Substituents possessing these characteristics typically include alkyl groups and unsaturated groups such as phenyl and cyano. An indication of relative stabilizing abilities of some substituents may be discerned from the bond dissociation energies, the energies required to form the radicals, listed in the below table.

Table 2. Bond Dissociation Energies[29] of Various Hydrocarbons (Kcal/mol).

R·	D(R-H)
CH_3-H	104
CH_3CH_2-H	98
$(CH_3)_2HC$-H	95
ϕ-CH_2-H	78
CH_2=CH_2CH_2=CH_2CH_2-H	80
NC-CH_2-H	79

Bond dissociation is an indication of the ease with which the bond is broken forming a pair of radicals. Thus these energies reflect the stability of the resultant radical. The substitution of a methyl for a proton increases the ease with which the radical is formed by approximately 6 Kcal/mol, whereas a phenyl substituent lowers the energy required by approximately 26 Kcal/mol. Alkyl groups do lower the energy required to break the bond but substituents that are able to delocalize the radical have a much greater stabilizing influence and a much lower homolysis energy. The selective use of such resonance stabilizing substituents can considerably lower the energy of the diradical intermediate, and therefore lower the energy necessary to form the substituted diradical intermediate (lower E_{a1}).

Alternatively, the activation energy (E_{a1}) can be decreased by increasing the energy of the starting material.

Increasing the energy of reactants

The idea is to start with a less stable, higher energy starting material which will react in a more facile manner. If the energy of the starting material is raised along with an equal increase in energy of the transition state, no change in the activation energy will result; there is only a simple upward energy translation of the reaction coordinate. The ideal situation is if the energy of the starting material is raised, but the energy of the transition state and the intermediate remains the same as, or becomes lower than, the energy corresponding to the analogous non-activated species. Thus the energy necessary for intermediate formation (E_1) will be lower than that for the nonactivated system.

Such an ideal situation exists with allene. The ground state energy of allene is higher than that of a simple olefin, and yet the stability of the transition state is significantly lower in energy than that of a corresponding olefin. It takes less energy to remove an electron from the reactive allene than it does to remove an electron from a more stable analogous olefin.[31] This is due in part to the fact that initial carbon-carbon bond formation occurs almost exclusively at the center carbon of the allene,[32] thus forming a radical alpha to a double bond. Initially this singly filled radical orbital is orthogonal to the two adjacent pi orbitals, but subsequent facile[33] rotation of the methylene group occurs forming a highly stabilized allyl radical (Figure 14).

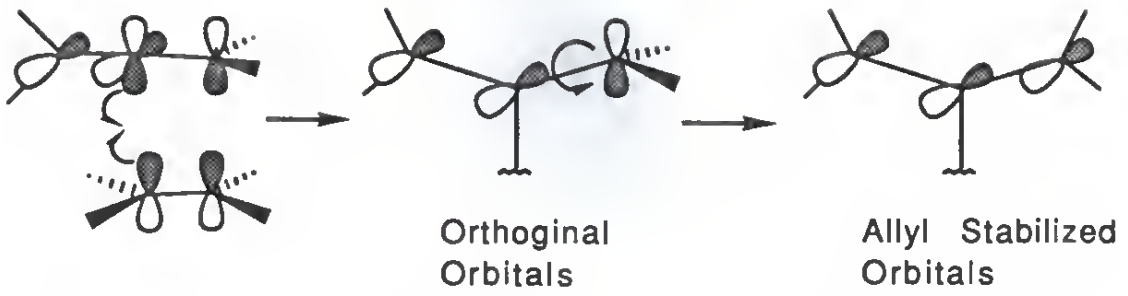


Figure 14. Rotation of Methylene forming Allyl Stabilized Radical.

This allyl stabilized 1,4 diradical is much more stable than a non-allyl stabilized radical. The degree to which a conjugated double bond stabilizes a radical can be approximated by the difference in bond dissociation energies between propane and propene. In both cases a sp^3 proton-carbon bond is being cleaved from the terminal carbon of a three membered chain to form a radical. The difference lies in the fact that one radical will be resonance stabilized and the other will not.

Olefin	Diss. Energy
CH_3-CH_2-CH_2-H	98 Kcal/mol
CH_2=CH-CH_2-H	87 Kcal/mol

Thus the allyl stabilized radical intermediate from allene is lower in energy by approximately 9 Kcal/mol than an analogous olefin.

The increase in reactivity of the allene can be attributed in part to the instability of the sp^2-sp-sp^2 configuration of the allene moiety. Enthalpies of hydrogenation of similar systems are able to illustrate this instability.[34] In the hydrogenation of both propene and allene, one p bond is being reduced to a σ bond. In the propene

system, two sp^2 carbons are being rehybridized to sp^3; in the allene system, one sp^2 carbon is becoming sp^3 and one sp carbon is becoming sp^2.

Olefin	DH_{hyd}(Kcal/mol)
Propene	-29.8
Allene	-35.3

An additional 5.5 Kcal/mol is resultant from the destruction of one of the strained p bonds of allene rather than the similar p bond in propene. This is a significant energy boost to further induce the formation of the diradical intermediate.

Another example of an increase in starting material energy resulting in an enhanced reactivity toward [2 + 2] reactions is the methylenecyclopropane system. The ground state energy of methylenecyclopropane is significantly greater than that of the open chain analog 1,1-dimethylethane. This is due to the unfavorable geometry the sp^2 hybridized carbon is forced to assume. The optimum bond angle of the sp^2 carbon is 120°, whereas the bond angle within the cyclopropane ring is only approximately 60°. The sp^2 hybridized carbon would much rather exist in a sp^3 hybridized state with a bond angle of 109°. There exists a substantial thermodynamic advantage for the destruction of the p bond. Such a transformation would occur if the methylenecyclopropane were to undergo a [2 + 2] reaction and form a diradical intermediate. Thus, methylenecyclopropane is abnormally reactive toward [2 + 2] cycloaddition reactions.

In summation, the lowering of E_1 can be accomplished by two general methods. The first method involves stabilization of the diradical intermediate, which is commonly done by the incorporation of resonance stabilizing substituents onto the olefin. Alternatively, in the second method, the activation energy barrier can be lowered by increasing the energy of the starting material. This is achieved primarily by the use of methylenecyclopropane or allene.

Much general knowledge exists concerning the [2 + 2] cycloaddition reaction, such as the precise means whereby this normally low yield reaction can be induced to occur. However, very little is known of the mechanism's internal intricacies. The vast majority of the mechanistic studies which have been performed on the [2 + 2] system have focused on the overall outcome of the reaction. The reaction products have been examined without investigating the intermediates particular behavior. Some of this lack of knowledge can be attributed to the difficulty and effort required in order to elucidate the interactions of any highly reactive dynamic intermediate.

Efforts have been directed at clarifying the behavior of diradical intermediates. Most of these studies have proceeded by independently generating 1,4-diradicals and analyzing the resultant products. The difficulty with this approach lies in the fact that diradicals have a reaction pathway predisposition[34] resulting from the particular manner in which they were formed (Figure 15).

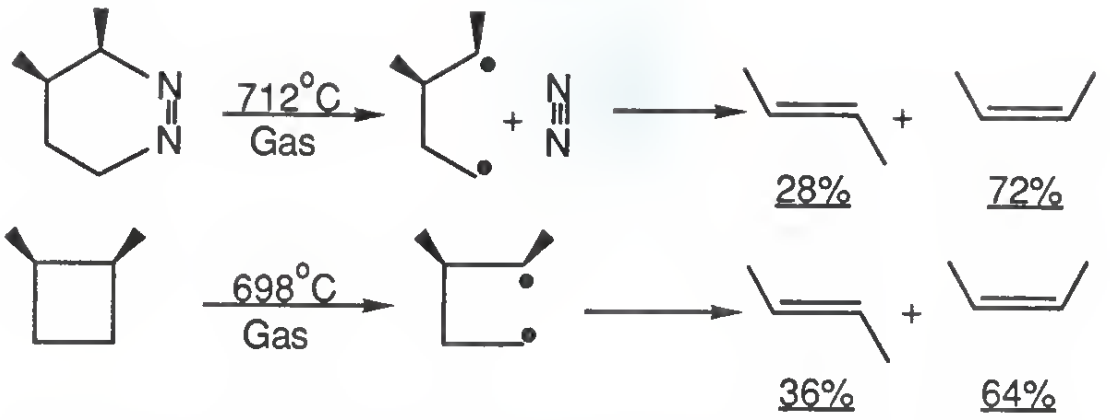


Figure 15. Stereochemistries of 2-butene from different sources.

Diradicals formed by different means have different energetics and display different reaction profiles. Artificially generated diradicals cannot be expected to have the same reactivity, nor can they necessarily be expected to behave in the same manner as the diradicals formed naturally during the course of a cycloaddition reaction. Thus, independently formed diradicals lend only subjective knowledge to a true diradical intermediate's behavior.

In order to ensure the investigated interactions of the diradical intermediate is a valid representation of the authentic [2 + 2] system, the parent [2 + 2] system itself must be studied.

The choice of the particular system to be studied is critical. The system must be chosen based on its ability to yield the most insight into mechanism while also keeping in mind the factors necessary to induce the reaction to proceed in reasonable yields.

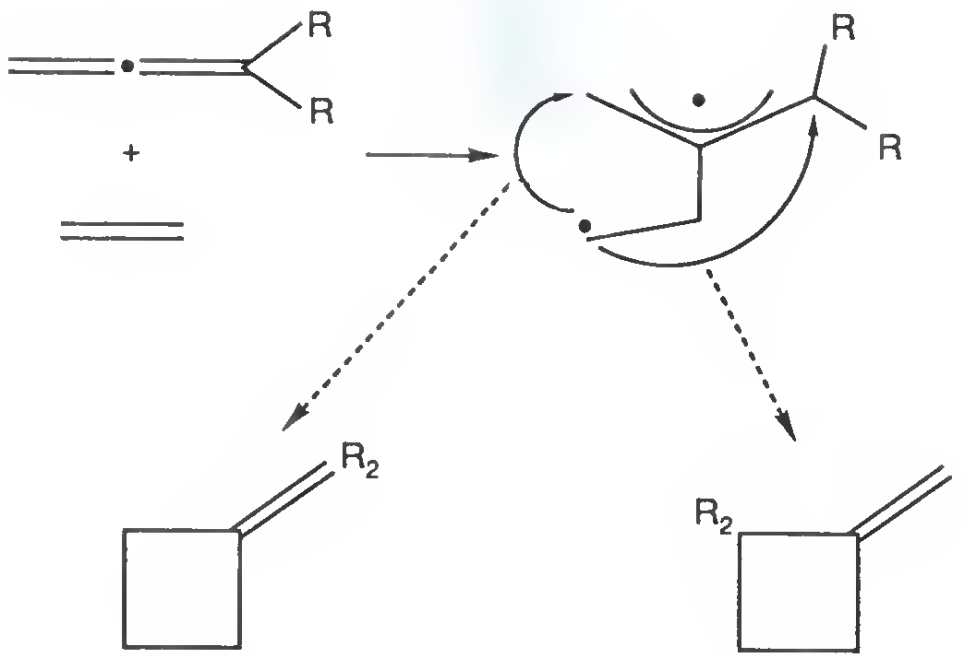
Allenes quite readily undergo [2 + 2] cycloadditions and they also provide an access into a unique mechanistic probe. The use of an

allene permits the study of the competition between two intramolecular paths of cyclization.

Allenes

Allenes undergo initial carbon-carbon bond formation almost exclusively at the center carbon of the allene.[31] This forms by rotation of the methylene, a highly stabilized allyl radical. The resulting allyl radical is able to undergo cyclization with either allyl terminus. If both allene termini are identically substituted, the competitive combination between either allyl end will be entirely random, dependant only on the fortuitous proximity of either allene terminus to the 4 position radical at the time of ring closure. The use of an unsymmetrically substituted allene allows by way of the product regiochemistry, direct detection of the competitive cyclization. The substituted terminus can bind with the 4-position radical to form an endocyclic substituted methylene cyclobutane product. Alternatively, the non-substituted terminus can combine with the 4 position radical to form an exocyclic substituted methylene cyclobutane product (see Figure 16).

The use of substituents on allene bring forth added factors affecting the competition. The regiochemical balance can be expected to be influenced by both electronic and steric effects. Some substituted allene systems have been well studied and the above mentioned effects are reasonably well understood.



Exo Endo

Figure 16. The Two Possible Regiochemistries from the Cyclization of an Unsymmetrically Substituted Allene.

A discussion of selected allene substituents will be postponed in order to review one possible dilemma associated with allene use in [2 + 2] cycloaddition reactions.

Concerted ketene cycloaddition

Although the concerted [2 + 2] cycloaddition reaction is symmetry forbidden, it is believed that ketene often adds in a concerted manner.[36] The cycloaddition of cis 2-butene with ethoxyketene results in a cis stereochemistry of all substituents in the product cyclobutane.

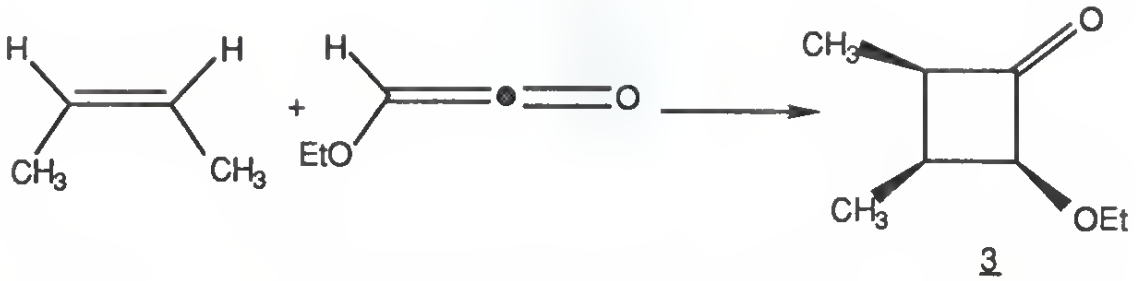


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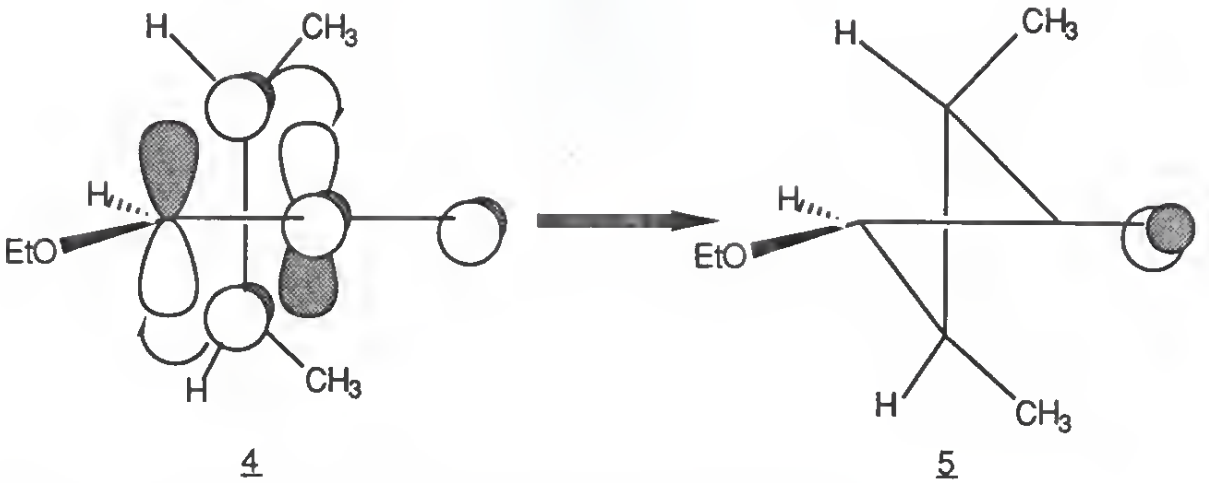
Figure 17. The stereochemical outcome of ketene and cis 2-butene.

If this addition occurred in a stepwise manner, a stereo scrambling of all substituents would be expected, with an abundance of the thermodynamically favored trans conformation resulting.

The observed stereochemistry is explained by invoking a concerted mechanism.

Using traditional approach trajectories, the concerted cycloaddition is symmetry forbidden, but because the ketene lacks any C_2 steric hindrance, the ketene has the option of approaching the butene in a variety of orientations. The use of Frontier Molecular Theory simplifies the analysis of allowable orientations. FMO states that in order for a reaction to be allowed, there must exist a positive orbital interaction between the Highest Occupied Molecular Orbital (HOMO) of one molecule and the Lowest Unoccupied Molecular Orbital (LUMO) of the other molecule. Examination of the LUMO of the ketene and the HOMO of butene reveals that an orientation with the ketene straddling the butene is symmetry allowed. This addition consists of the π bond of one molecule descending across the π orbital of another molecular orbital. The LUMO of the ketene is able to lay across the HOMO of the butene, resulting in complimentary orbital phase overlap with good spatial proximity.



4 5

Figure 18. Orbital Orientation in a Concerted Ketene Cycloaddition.

The orbital orientation of reactants (4) is such that all steric interactions are minimized.The methyl groups on the olefin are oriented toward the less sterically crowded oxygen end of the ketene. The methoxy substituent on the ketene is directed away from the butene. As the bonds are established, the relative substituent configuration is preserved, and the final skewed box product (5) is formed. As the box (5) is "unfolded" one can see the substituent orientation is identical to that observed in 3 (Figure 17). This concerted addition orientation reasonably explains all of the observed product stereochemistry, and additionally is symmetry allowed.

These same arguments are valid when applied to an analogous allene system. There exists some documented support for a concerted [2 + 2] mechanism operating on allene systems. Pasto[36] heartily supported the concerted mechanism from a theoretical and experimental standpoint in 1979. But upon execution of more

detailed experiments, kinetic isotope effects, relative reactivities, and stereoselectivities, he revised his assessment of the situation and retracted his previous conclusions, three years hence,[38] in favour of a stepwise addition sequence. Although theoretically the concerted allene [2 + 2] cycloaddition is viable, extensive experimental evidence,[32,39] in particular substituent scrambling, has given no hard support for its occurrence.

Upon further consideration, it is quite interesting to note that the theoretically possible concerted [2 + 2] cycloaddition is not what's experimentally observed. Yet, the stepwise addition, proceeding through a high energy diradical intermediate, proceeds relatively well if the proper activating substituents are present.[13]

This is another example of the lack of precise knowledge associated with the [2 + 2] cycloaddition reaction mechanism. Which brings us back to the problem at hand; the thorough understanding of the operating mechanism. In order to gain as much insight as possible into the investigation of the [2 + 2] reaction mechanism, the choice of the properly substituted allene is critical.

Difluoroallene

The choice of difluoroallene as the unsymmetrically substituted allene to be used has many advantageous facets. The energy of activation of the initial bond formation (E_{a1}) is lowered by the use of an allene. In addition, the employment of a gem-difluoromethyl group brings about a large thermodynamic preference to exist in a sp^3 hybridization. Thus, the energy of activation of the

cyclization step (E_{a2}) is lowered, and the forward cyclization will be favored over the reverse bond homolysis ($E_{a2} << E_{a-1}$). In fact it has been experimentally demonstrated that when using difluoroallene, bond cleavage is not competitive with cylization.[39]

As earlier discussed, fluorine has a very small radius and therefore elicits little steric demands. No steric impediment toward cyclobutane formation will result from using fluorine as a substituent. All these facets combine to make difluoroallene quite reactive to [2 + 2] cycloaddition reactions. In fact the additive effect of these factors are responsible for allene being more reactive than propene, monofluoroallene being more reactive than allene, and difluoroallene being more reactive than monofluoroallene.[40]

Furthermore, difluoroallene itself has been reasonably well studied. Both photoelectron spectral studies and ab initio calculations have been performed. It was found that fluorine with its intense electronegativity, pulls a great deal of electron density through the sigma bonds. Concurrently, fluorines orbital size matches so well with that of carbon, that fluorine donates a substantial electron density into the pi molecular network. The theoretical *ab initio* studies performed by Houk[30] predict that the pi-electron-donating and sigma electron-withdrawing characteristics of the gem difluoro group work simultaneously on different orbitals. The result is an electron rich π C_1-C_2 double bond which is similar to allene, and a very electron deficient π C_2-C_3 double bond, similar to trifluoropropene.

The photoelectron spectroscopy study reveals real numbers for the magnitude of the orbital levels energies. Difluoroallene exhibits two very distinct orbital energies. This is in direct agreement with theory.

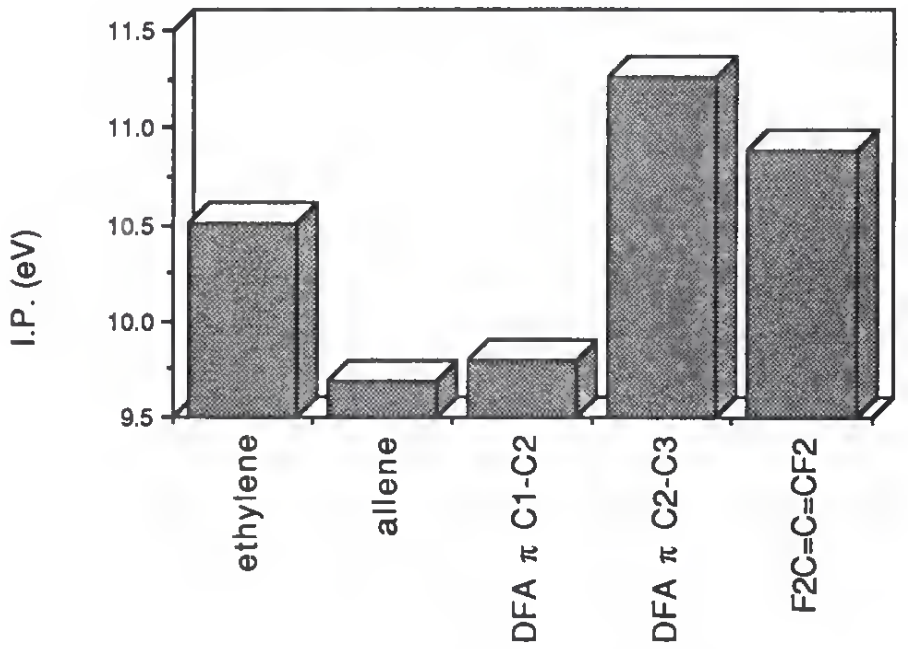


Figure 19. Ionization Potentials of Various Olefins.

It takes less energy to remove an electron from π C_1-C_2 than that which is needed to remove an electron from π C_2-C_3. The π C_1-C_2 electrons exist at a higher resting energy, and thus are less stable than the electrons in π C_2-C_3. A radical addition process effectively removes one electron from each molecule's pi orbital to make a new sigma bond. The orbital of difluoroallene from which an electron can most easily be removed from is the π C_1-C_2 orbital. Thus the initial carbon-carbon bond will occur at the center carbon, with partial

radical charge forming predominantly on the C1. The C_1 methylene then undergoes rotation to form the delocalized allyl radical.

This unsymmetrical substituted allyl radical then has the option of cyclizing in two direction to form either the endo- or the exocyclic difluoromethyl cyclobutane. The direct observance of competitive cyclization between either terminus can be made by analysis of product regiochemistry.

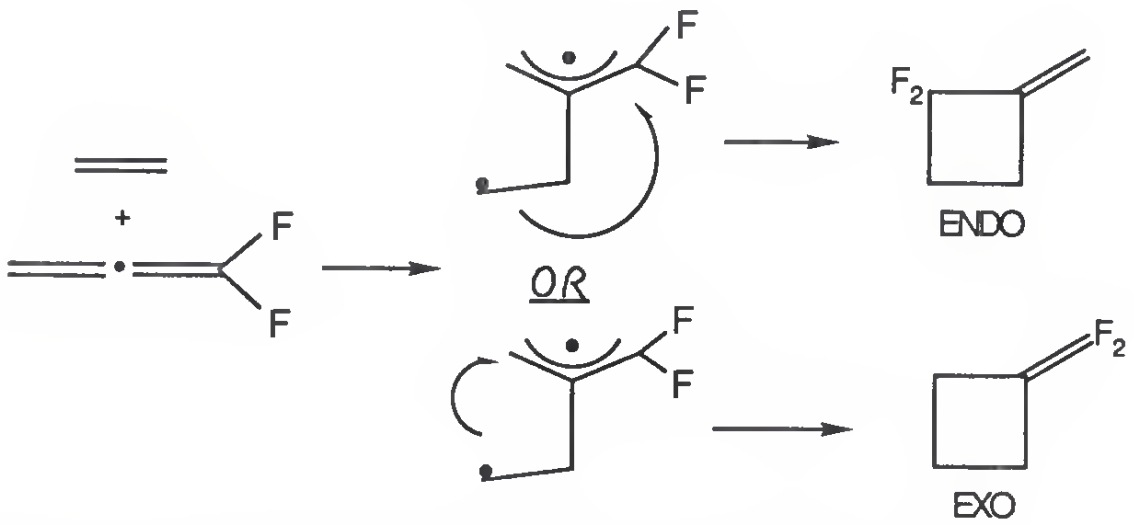


Figure 20. Possible Regiochemical Orientations of the Gem-Difluoromethyl Group.

Because of fluorine's small steric demands, the competition between either terminus is not complicated by steric demands. Furthermore, fluorine, like hydrogen has a spin quantum number of 1/2. This means fluorine is NMR active. Fluorine NMR is remarkably convenient to use due to the large difference in chemical shifts between very similar compounds i.e. cis and trans 1-fluoropropene exhibit a 1.9 ppm difference in chemical shift.[42]

Additionally, the high reactivity of difluoroallene allows a wide variety of counterolefins to be used in the cycloadditions. The use of a stereochemically labeled olefin with difluoroallene would permit both the regiochemistry and the stereochemistry of a [2 + 2] reaction to be monitored simultaneously. The study of how various steric and electronic perturbations effect the regiochemical and stereochemical outcome of the reaction, could yield valuable insight into the mechanism itself.

Stereochemistry

The stereochemical alterations which occur during the reaction can be monitored by using an isotopically pure starting material and analyzing the resultant product stereochemistry. The choice of the proper stereochemical label must take into account the availability of the stereochemically pure material and the ability of the material to readily undergo [2 + 2] cycloadditions. The use of deuterated styrene was chosen because it is both available and a good radical stabilized olefin.

Difluoroallene and Z-ß-Deuteriostyrene

Wicks and Dolbier[42] utilized the same Z-ß-deuteriostyrene to study the thermal regio- and stereochemical permutations of the [2 + 2] cycloaddition reaction. The stereochemical transformations occurring during the reaction may be determined by analyzing the resultant product stereochemistry. The phenyl and deuterium substituents enter into the reaction in the pure zusammen

conformation, they may retain this conformation over the course of the reaction, or may undergo a conversion to the entgegen orientation.

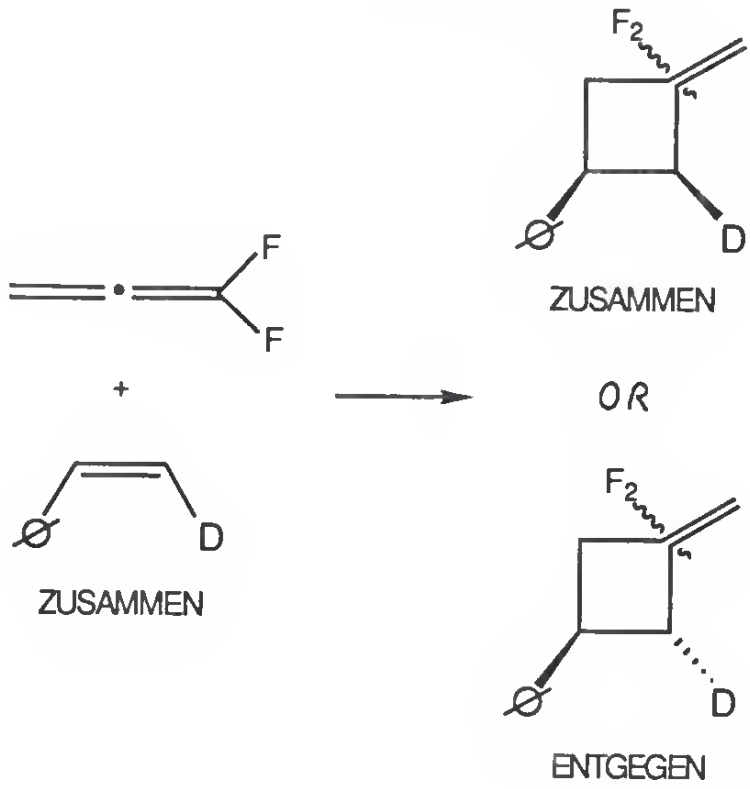
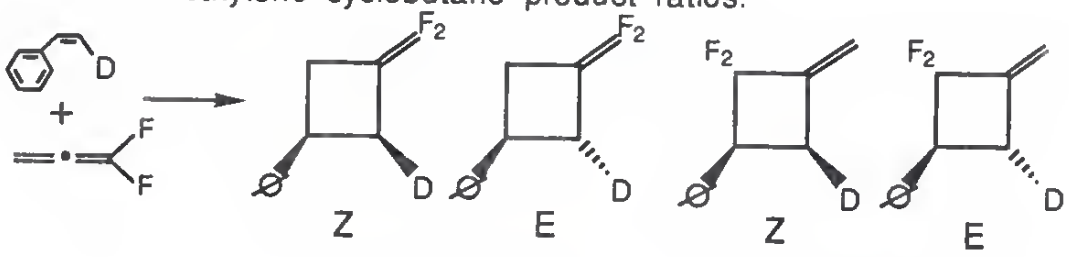


Figure 21. Possible Stereochemical Outcome from Z-ß-Deuteriostyrene.

The product regiochemistries and stereochemistries were previously determined from this reaction over a temperature range of 70°C to 100° C. There are two possible regioisomers, endocyclic difluoromethylene and exocyclicdifluoromethylene. There are also two possible stereoisomers, Z and E. The results are tabulated below. The true reaction mixture will contain a mixture of

enantiomers. An enantiomeric separation was not performed, the results are based on these racemic mixtures, but for clarity only one enantiomeric scenario is represented.

Table 4. Methylene cyclobutane product ratios.



100° C	79 : 21 (19)	57 : 43 (81)
80° C	79 : 21 (18)	58 : 42 (82)
70° C	79 : 21 (17)	59 : 41 (83)

Although essentially no change occurred over the temperature range studied, the interesting and important point to note that the two regioisomers possess different stereochemistries! This fact necessitates the incorporation of another intermediate into the diradical mechanism. In order to adequately explain the differing degrees of stereochemical retention, there must exist two kinetically distinct intermediates. If only one intermediate were present, the stereochemistry of that intermediate should be expressed identically in each of the regiochemical products fathered by that intermediate (Figure 22).

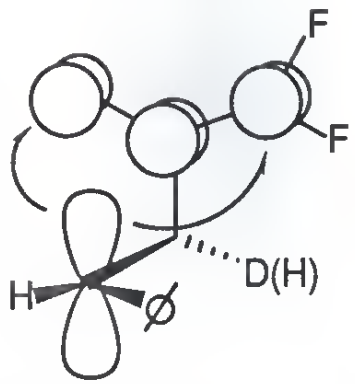


Figure 22. A Single Intermediate Proceeding to both Endo- and Exocyclic Regiochemical Products.

For instance, if the single intermediate existed with 70% of deuterium in the Z orientation, then all of the endo- and all of the exocyclic difluoromethylene products originating from this intermediate would similarly possess a 70% Z orientation of deuterium to phenyl. This is <u>not</u> what is observed, therefore a simple single intermediate does not account for the observed results and therefore a single intermediate cannot be present. What is proposed, which can account for all of the stereochemical inequalities, is the presence of two conformationally divergent intermediates. The initial intermediate has two possible reaction paths; it can either cyclize to form products possessing the identical stereochemistry as the parent intermediate, or alternatively, this initial intermediate can undergo a conformational alteration to become a kinetically distinct second intermediate. This second intermediate will possess a separate unique stereochemical configuration. The cyclobutane products produced from this second intermediate will have the same stereochemical makeup as their precursor

intermediate, and different from the stereochemical composition of the products produced from the first intermediate.

The reason for the different regiochemical products having different stereochemical configurations, is that the different intermediates have different regiochemical preferences when closing. Intermediates 1 and 2 possess unique stereochemical orientations and each close in different regiochemical ratios. Thus the total stereochemistries of the endo and exocyclic products, are expected to, and do posses, different degrees of stereochemical retention. A very simplified mechanistic scheme depicting these characteristics follows.

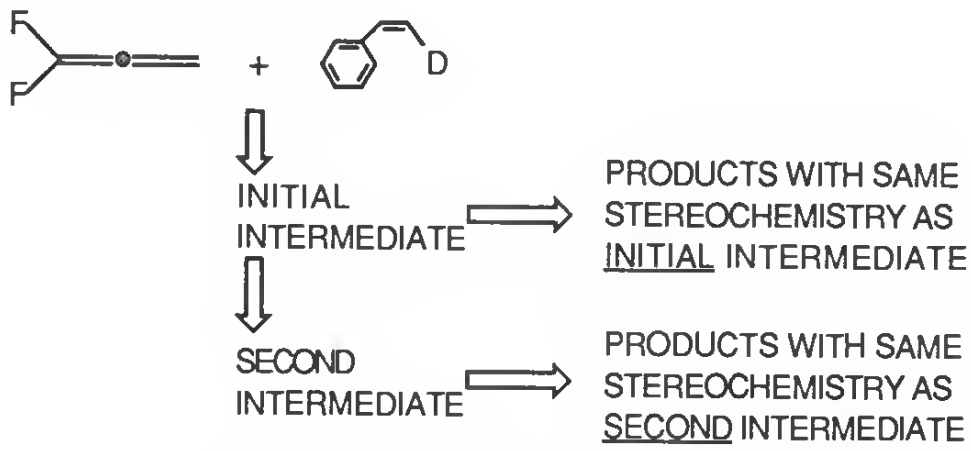


Figure 23. Generalized Reaction Mechanism Scheme.

The specific mechanism which was proposed (Figure 25) consists of the difluoroallene reacting with the styrene as earlier described, with initial bond formation occurring at the center carbon of the allene. This is followed by immediate methylene rotation, forming an allyl radical. This highly reactive initial intermediate

(I_1) is conformationally very reactant like, it can thus be expected that little stereochemical scrambling has yet occurred. Upon I_1's cyclization the resulting products will subsequently possess a very high degree of stereochemical retention. But because this species is so reactive, it is expected very little regioselectivity will be observed during ring closure. Thus, it is proposed the products formed from I_1 will possess a great deal of stereochemical integrity and a distinct lack of regiochemical partitioning.

Alternatively this initial intermediate (I_1), can undergo a rotation about the C_3-C_4 bond, this rotation can be expected to occur by the unfavorable steric interactions of the phenyl group with the C_3 hydrogen. This second intermediate (I_2) due to the reduction of steric strain, should be lower in energy, less reactive, and much longer lived than the first intermediate (I_1, see Figure 24).

The more stable, longer lived intermediate (I_2) has little steric constraints prohibiting rotation about it's C_2-C_3 bond. Once this rotation occurs, all stereochemical integrity is lost. Any cyclization occurring after this rotation in this intermediate would possess no stereointegrity; essentially 50% Z and 50% E orientation of deuterium and phenyl substituents should result.

The regiochemistry of this second intermediate is also expected to be different from that of the first intermediate. The more stable the intermediate, the greater degree of selectivity that intermediate will possess. A substantial thermodynamic energy

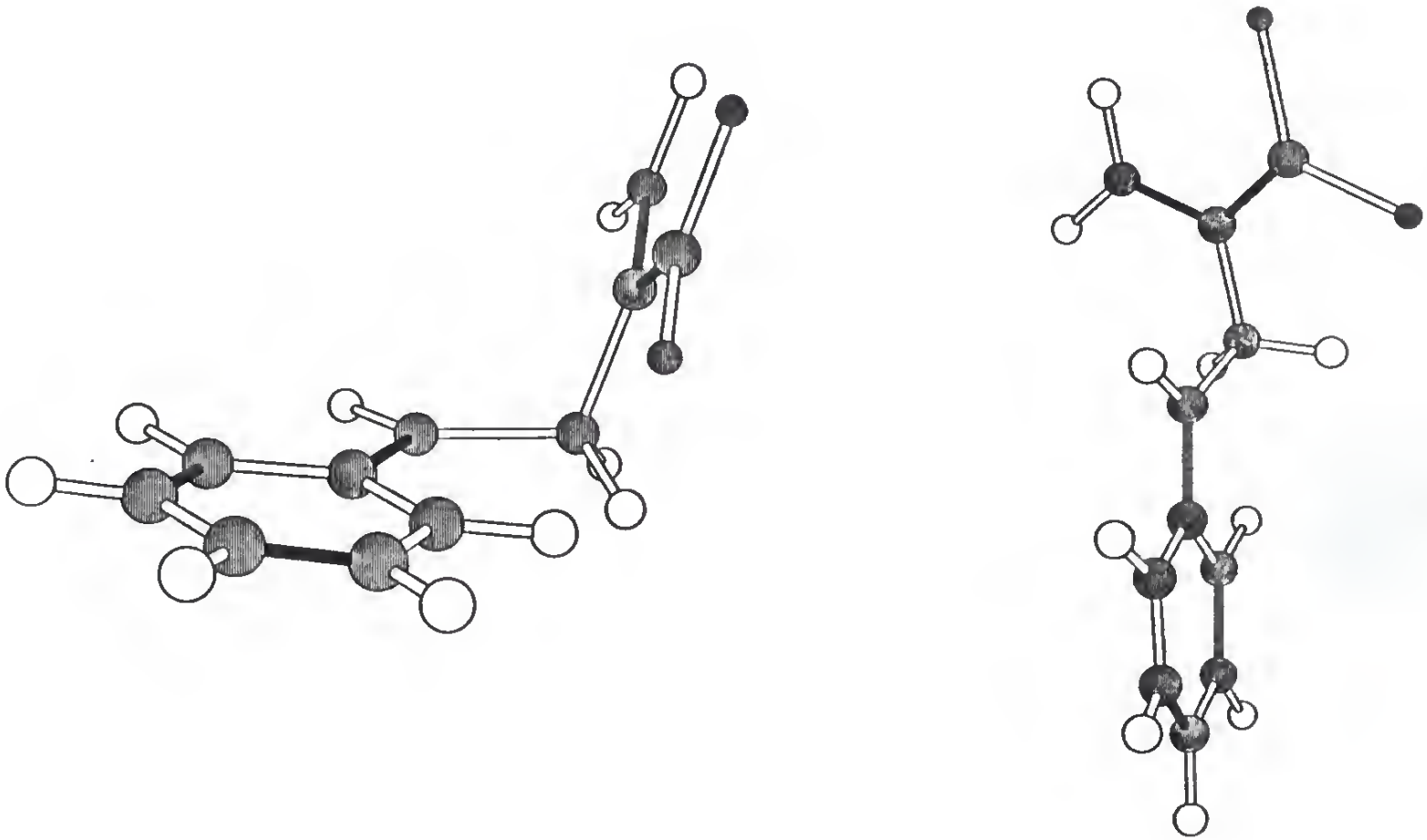


Figure 24. Initial and Second Intermediate from the [2 + 2] Cycloaddition of Styrene and Difluoroallene.

difference exists between the two possible product regioisomers, the difluoromethyl group prefers the endocyclic orientation by approximately 5 Kcal/mol. The second intermediate is expected to be significantly more stable, and further along the reaction coordinate, than the initial intermediate. Thus, it is expected the second intermediate (I_2) will produce a greater amount of the more stable product, the endocyclic 2,2-difluoromethylenecyclobutane, than the initial intermediate (I_1). The products originating from the second intermediate are therefore expected to possess a high degree of regioselectivity and a low degree of stereoselectivity.

The proposed reaction scheme is detailed in Figure 25. For simplicity, only one enantiomeric scenario has been represented, but the other enantiomeric analog also exists.

It is important to note that this mechanism was based on no concrete evidence. The presented mechanism was simply the best conceived scenario to explain the observed phenomena.

There existed an intense desire to more fully characterize this mechanism; to test the above hypothesis and to more fully probe the dynamics and intricacies of the reaction. Some fundamental difficulties hinder the facile elucidation of this mechanism. First as documented earlier, this reaction is relatively insensitive to temperature variation. Essentially no stereochemical change occurred over the thirty degree temperature range previously studied. The problem with merely expanding this temperature range studied is that at lower temperatures the reaction simply doesn't occur. At higher temperatures the selectivity, the facet which

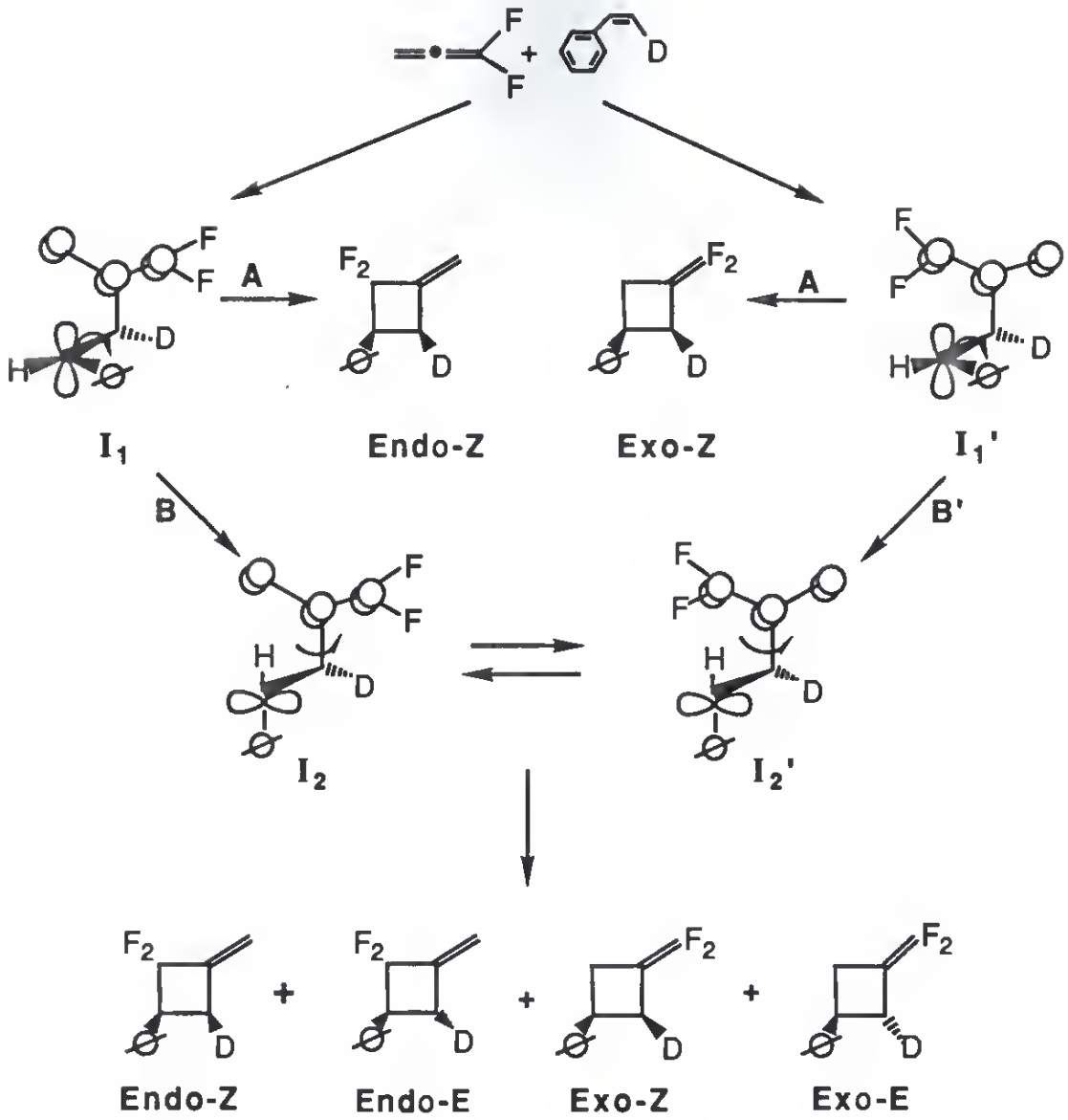


Figure 25. Detailed reaction mechanism accounting for observed regio- and stereochemical product ratios.

makes this entire discussion interesting, is decreased. There exist other problems with the traditional substituent altering modes of mechanistic probing in that the [2 + 2] reaction. Many olefins will simply not undergo such a cycloaddition. Bulky substituents on

olefins induce cycloaddition to proceed at such a slow rate that the predominant reaction products become dimers and oligomers of difluoroallene. Thus, a subtle non-destructive, not overly perturbing method of inquiry was desired. The utilization of high pressure was selected as the method of choice to carry out these chosen experiments.

High Pressure

The impetus for using high pressure can be illustrated with the two following fundamental thermodynamic equations.[44]

$$\Delta G^{\circ} = -RT \ln k \qquad \text{and} \qquad \left(\frac{d\ \Delta G^{\circ}}{d\ P}\right)_T = V^{\circ}.$$

Differntiating the first equation with respect to pressure lends the following equation:

$$\frac{d\ \Delta G^{\circ}}{RT d\ P} = \frac{-d \ln k}{d\ P}$$

Substituting the transition state analogy of the second equation yields

$$\boxed{\frac{-\Delta V^{\neq}}{RT} = \frac{d \ln k}{d\ P}}$$

R is Rydberg's constant, T is temperature, k is the rate constant, and $V^{\neq}$ is the volume of activation. The volume of activation ($V^{\neq}$) is

one of the few intrinsic properties of the transition state that can be accurately and easily measured.[45] It is equal to the effective difference in volume between the starting material and the transition state. This overall change in volume is dependent on both change in volume resulting from the degree of solvent ordering($\Delta V^{\neq}_{sol}$), and the inherent difference in volume directly attributed to changes in molecular volume ($\Delta V^{\neq}_{rxt}$).

From the above boxed equation, it follows a reaction having a negative volume of activation, when subjected to an increase in pressure, will subsequently undergo an increase in reaction rate. Cycloaddition reactions which proceed from two distinct starting molecules to one transition state species, typically have a substantial negative volume of activation. The Diels-Alder reaction of maleic anhydride and cyclohexadiene has a volume of activation equal to -37.2 cm^3/mol.[44] A reaction having a volume of activation equal to -30 cm^3/mol, when subjected to 10 kbar of pressure will experience a 2 x 10^5 increase in rate. One bar of pressure is equal to 0.987 atmospheres or 14.5 p.s.i. Ten Kbar is equal to 9,870 atmospheres or 145,000 p.s.i.

The application of pressure brings about a rate increase which is in proportion to the negative volume of activation of that reaction. If a system has two available paths of reaction, with differing volumes of activation, the application of high pressure will most greatly enhance the path having the most negative volume of activation. Thus, the application of pressure, along with increasing the overall rate of reaction, causes an increase in

reaction selectivity, favoring the path with the lowest volume of activation. This is in direct contrast to thermally increasing the rate of a reaction which causes a general decrease in selectivity.

In order to test the hypothetical mechanistic scenario, the effects of pressure can be predicted based on this reaction, then the reactions can be carried out, and the results compared with the predictions. If the expectations are realized in the experiments, substantial support for the proposed mechanism will be gained.

CHAPTER TWO
THE HIGH PRESSURE EFFECT ON THE [2 + 2] CYCLOADDITION OF Z-ß-DEUTERIOSTYRENE AND DIFLUOROALLENE

Introduction

The fact that different regiochemical products, endo- and exo-difluoro substituted cyclobutanes, possess different degrees of stereochemical retention prompted an interest in determining the precise mechanism of the [2 + 2] cycloaddition. The results necessitated a mechanism with two kinetically distinct intermediates. Although the mechanism which was proposed (figure 21) logically explains the observed inequality of stereochemistry, it was based on no direct physical evidence. In an effort to ascertain the true operating mechanism, a more thorough series of studies was directed at verifying or refuting this proposed mechanism.

It was decided to test this mechanism by making certain predictions on how this mechanism would respond to a given set of conditions. The system would then be subjected to these conditions and the experimental results compared with the predictions.

The chosen imposed condition is high pressure. The predicted high pressure effects can be easily assessed by a logical analysis of the mechanism.

The initial diradical forming step has an associated negative volume of activation. Remembering that the application of pressure facilitates reactions with negative volumes of activation, this

initial step will experience a rate enhancement when subjected to a pressure increase. Because this step is the rate determining step, an overall increase in reaction rate is expected to be seen with an increase in pressure. This initial step precedes the divergence between competing paths, therefore at this point in the reaction path pressure will elicit no influence on path differentiation. Once this diradical is formed (I_1, Figure 25) two pathways become accessible. Path A, immediate ring closure where two free ends of a molecule bind together to form a closed system, can be easily envisioned as having an inherent decrease in overall volume. Cyclizations are known to posses negative volumes of activation.[46] This decrease in volume indicates a negative volume of activation and the application of pressure should therefore facilitate this pathway.

As discussed earlier, the immediate closure of the initial diradical intermediate to products should coincide with a high degree of stereoselectivity and low degree of regioselectivity. This is due to the fact that this first intermediate is very reactive; it's energy well is very shallow. Alternative paths emanating from a shallow energy well cannot have a great deal of energy difference between them. Thus the highly reactive diradical intermediate should not show a distinct preference for either regiochemical cyclization pathway, and therefore pathway A should show a lack of regioselectivity. This high reactivity also makes it reasonable to expect little stereochemical rearrangement has occurred by the time cyclization has taken place, therefore products from path A are

expected to have a high degree of stereochemical retention. The products from path A should show little regioselectivity but should display a high degree of Z orientation of the phenyl and deuterium substituents.

The second available pathway, path B, consists of the initial intermediate undergoing a conformational rotation about the C_3-C_4 bond, to form the second intermediate. This rotation of the phenyl group down out of the plane of the molecule, greatly reduces the phenyl groups 1,4 steric interactions. This process can be easily envisioned as being concurrent with an increase in volume[45] (figure 24), in which case the activation volume of this transformation should be positive. Therefore this process (step B) should be retarded by pressure. The resulting second intermediate will be considerably lower in energy and thermodynamically more stable than the first intermediate. This decrease in reactivity leads to an increase in selectivity. The second intermediate is expected to exhibit a distinct preference of the difluoromethyl allyl terminus to be directly involved in the cyclization, and should therefore form an excess of the more thermodynamically stable endo-difluoromethylenecyclobutane product. After this second intermediate is formed, free rotation about the C_3-C_4 bond becomes possible, and if this does occur, all of the systems stereointegrity is lost. Overall, path B is predicted to be retarded by pressure, to have a characteristic lack of stereoselectivity, and to have a significant amount of regioselectivity. The products from path B are therefore predicted to be composed predominantly of the

endo-difluorocyclobutane having scrambled deuterium and phenyl substituents.

In summation, path A is proposed to be favored by the application of pressure and to proceed with a high degree of stereochemical retention but a low degree of regioselectivity. Path B is expected to be disfavored by pressure and to proceed with a low degree of stereochemical retention but with a substantial degree of regioselectivity.

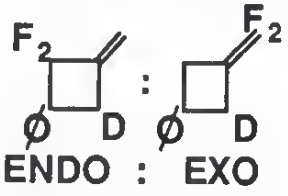
The performance of these high pressure experiments and the comparison of the resulting experimental product stereochemistry and regiochemistry with the stereo- and regiochemistries predicted based on our proposed mechanism, will allow this mechanism to be either supported or discredited.[46]

Results and Discussion

All high pressure experiments were carried out by condensing difluoroallene(6) into low-density polyethylene tubes containing degassed Z-ß-deuteriostyrene(7). This is followed by flame sealing the tubes and pressurizing using a high pressure apparatus (a thorough discussion of the high pressure apparatus used throughout this work can be found in appendix B). Reaction times varied from 0.5 to 134 hours, depending upon the time required for the reaction to proceed to completion. The regiochemical product ratios were determined by a minimum of 4 corroborating injections on a F.I.D./G.C.. The individual regioisomers were separated by prep G.C., and the stereochemistry of these individual regioisomers were

determined by quantitative ^1H 300 MHz N.M.R.. The results from these experiments are presented in the table below.

Table 4. Product Ratio Dependence on Pressure



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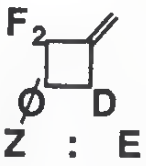

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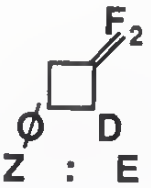

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Pressure (Kbar)	Regiochemistry	Stereochemistry	
13.0	69.6 : 30.4	85.5 : 14.5	95.2 : 4.8
11.0	70.6 : 29.4	83.2 : 16.8	94.6 : 5.4
8.0	77.7 : 22.3	74.5 : 25.5	92.3 : 7.7
5.9	82.1 : 17.9	73.2 : 26.8	91.2 : 8.8
4.1	84.1 : 15.9	71.6 : 28.4	89.9 : 10.1
1.8	86.1 : 13.9	66.3 : 33.7	88.0 : 12.0
±0.06	±0.05%	±0.16%	±0.67%

In contrast to the very constant ratios obtained from variable temperature studies,[42] dramatic changes in stereo and regiochemical ratios occur with the application of high pressure. It is evident that as the pressure is increased, the regioselectivity is reduced and the stereoselectivity is greatly enhanced. As the pressure is increased from 1.8 Kbar to 13 Kbar a marked decrease in regioselectivity results. At 1.8 Kbar the product mixture is composed of 86% of the

endocyclic isomer whereas at 13 Kbar this is reduced to 70%. There also exists a striking increase in stereoselectivity with pressure, culminating at the point of 95.2% retention of configuration occurring at 13 Kbar for the minor isomer. These observed trends are exactly that which were proposed based on the previously proposed mechanism. The near linear dependence of regioselectivity with pressure is illustrated by the below plot.

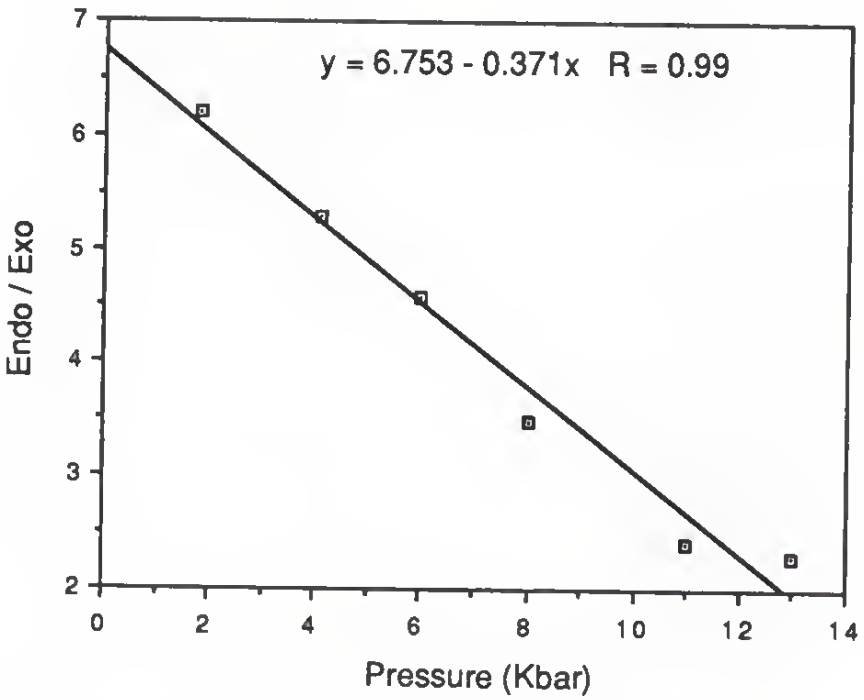


Figure 26. Pressure Dependence on the Regioselectivity of Cyclization between Z-ß-Deuteriostyrene(7) and Difluoroallene(6).

The observed trends are consistent with the imposition of high pressure giving rise to an increase in path A which is less regioselective and more stereoselective than path B. These high

pressure results give substantial support to the proposed mechanism. They substantiate the hypothesis of an initially formed highly reactive intermediate which can either undergo cyclization with high stereoselectivity and low regioselectivity, or can conformationally convert to a less reactive second intermediate. This second intermediate in turn undergoes cyclization with a high regioselectivity and a low stereoselectivity. The cyclization of the first intermediate is expected to posses a significant negative volume of activation, in contrast the conformational conversion (path B) is expected to have a slightly positive change in volume.[45]

Stereochemistry

Step A was proposed as proceeding with 100% stereoselectivity, in view of the fact that at 13 Kbar, a 95% retention of stereochemistry results for the minor isomer, this proposal has a high probability of being valid. If step A is 100% stereospecific, all of the stereoscrambled product must come from path B. Once the second intermediate is formed, rotation of the C_3-C_4 bond is known to result in stereorandomization, thus Path B has been assumed to proceed with 50% cis and 50% trans stereochemistry. Therefore for each observed percent of product having stereochemical inversion, and therefore from path B, there exists an equal percent of product having stereochemical retention also from path B. This information can be coupled with the degrees of stereochemical retention of products to yield the percent of products formed from each pathway.

For example, if a product mixture has 80% retention and 20% inversion of stereochemistry, this means all 20% of the inverted conformation is produced by path B along with an equal amount of the stereoretained product. Thus, 60% of product comes from path A and 40% comes from path B. Analogous calculations were carried out on all of these high pressure results.

Table 5. Calculated Percentages of Products formed from Pathway A and B.

Pressure (Kbar)	Percent of Total Product from A, B	Percent of Endocyclic(8) from A, B	Percent of Exocyclic(9) from A, B
13.0	76.9 : 23.1	71.1 : 28.9	90.3 : 9.7
11.0	73.1 : 26.9	66.3 : 33.7	89.3 : 10.7
8.0	56.9 : 43.1	49.0 : 51.0	84.6 : 15.5
5.9	52.8 : 47.2	46.3 : 53.7	82.4 : 17.6
4.1	49.1 : 50.9	43.3 : 56.7	79.9 : 20.1
1.8	38.7 : 61.3	32.7 : 67.3	76.3 : 23.7
	±0.5 ±0.5	±0.3	±1.3

This provides a quantified assessment of the competition between path A and path B. The pathway preference is influenced greatly by pressure. At 1.8 Kbar 38% of products are being formed by path A whereas at 13 Kbar it has risen to 77%. This is in direct contrast to varying temperature studies[2] where path A accounts for a constant 25%. This trend exactly parallels that based on expected volumes of activation. The contribution of path A is expected and does undergo a

great enhancement when subjected to high pressure. These results additionally demonstrate some of the advantages unique to high pressure chemistry.

Regioselectivity of Individual Paths

The initial assumption that path A proceeds with 100% stereoselectivity and B by 50%, allows the calculation of the amount of each individual regioisomer forming from each path. Knowing the amount of each regioisomer from each path allows, by simple division, the regioselectivity of each path to be calculated.

Table 6. Pathway Regioselectivity Dependance on Pressure.

Pressure (Kbar)	Regioselectivity (Endo:Exo) of Path A	Path B
13.0	64.3 : 35.7	87.3 : 12.7
11.0	64.0 : 35.9	88.3 : 11.7
8.0	66.9 : 33.1	92.0 : 8.0
5.9	72.0 : 28.0	93.3 : 6.7
4.1	74.1 : 25.9	93.7 : 6.3
1.8	72.6 : 27.4	94.6 : 5.4
	±0.5	±0.7

It may be initially expected that the regioselectivity of each individual path would remain fixed with changing pressure. Although the propagation of experimental errors has become quite large, these results still demand that the path regioselectivity is not constant but varies with pressure. In addition, the two paths undergo the

same incremental change in regioselectivity with pressure. They both undergo a change of approximately 7.5%. The cause may not be intuitively obvious. A plausible explanation is that as the pressure is raised the reactivities of all of the intermediates are raised. Therefore the cyclization of these intermediates becomes less selective at increased pressure, and a decrease in regioselectivity results.

Pathway Selectivity

It has previously been shown[43] that the cyclization steps are non reversible, thus the ratio of products from each path is equal to the ratio of the rates of these paths, (%product from A) ÷ (% product from B) = k_A/k_B.

Recalling from equation 1, that

$$\frac{\delta \ln k}{\delta P} = \frac{-\Delta V^{\neq}}{RT},$$

and realizing P, R, and T are the same for each path, one can take the difference of equation 1 as applied to both A and B and arrive with the following equation,

$$\frac{\delta \ln (k_A/k_B)}{\delta P} = \frac{-\Delta\Delta V^{\neq}_{A\text{-}B}}{RT}.$$

By plotting the ratio of product formed from path A and B verses pressure, one obtains a line with a slope equal to the difference in volumes in activation between path A and path B divided by R and T.

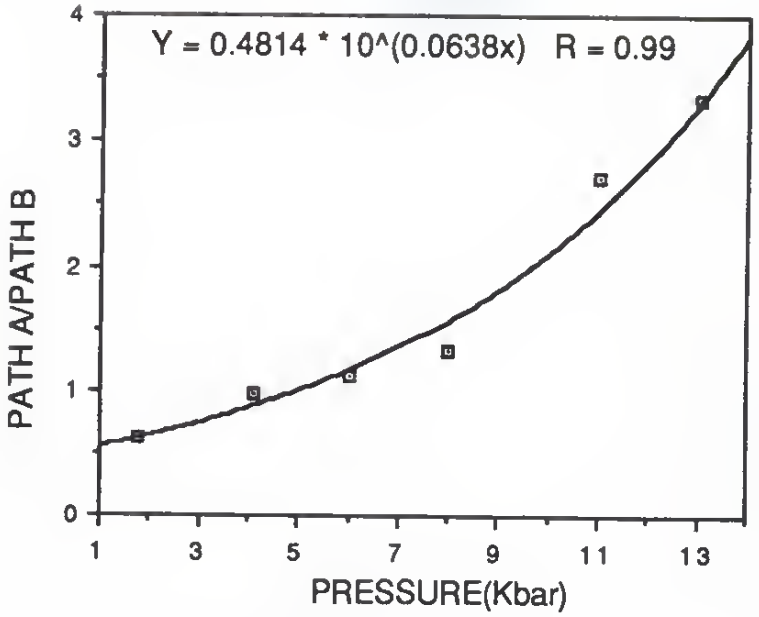


Figure 27. Pathway Dependance on Pressure.

From the above path selectivity dependance on pressure, and knowing $\frac{\delta \ln (k_A/k_B)}{\delta P} = -\frac{\Delta \Delta V^{\neq}_{A-B}}{RT}$, one is able to arrive at a definitive value describing the volume difference between the competing paths, A and B.

Y=A/B, X=Pressure

$A/B = 0.4814 * 10^{(0.0638\ P)}$

taking the ln of both sides:

ln A/B = ln 0.4814 + 0.0638 + ln 10.

ln A/B = -0.7311 + 0.1469 P

rearranging,

$$\frac{\delta \ln A/B}{\delta P} = 0.1469$$

Given $\frac{\delta \ln A/B}{\delta P} = -\frac{\Delta\Delta V^{\neq}_{A-B}}{RT}$, and substituting

$$0.1469 = -\frac{\Delta\Delta V^{\neq}_{A-B}}{RT},$$

with T =298 K and R = 0.08314 cm^3 Kbar/ K mol, one arrives at;

$\Delta\Delta V^{\neq} = 3.64\ cm^3/mol$

The difference in volume of activation between paths A and B is 3.64 cm^3/mol. We have arrived at a quantitative description of the difference between the two competing intramolecular steps within our reaction mechanism.

Viscosity Consideration

Divorcing pressure effects from viscosity effects cannot be accomplished. Viscosity is an integral part of pressure effects. The volume of activation is composed of both a $\Delta V_{solvent}$ and a $\Delta V_{intrinsic}$. A change in pressure results in a change in viscosity. Both pressure and viscosity individually influence reaction outcomes.

While it is not our goal to quantitatively determine the magnitude of the exact viscosity contribution, it is certainly in our best interest to qualitatively understand the influence viscosity has in determining reaction outcome. The combination of the viscosity influence on regioselectivity and the pressure impact on viscosity, with the high pressure regioselectivity, can provide a foothold into

understanding the degree to which viscosity is involved in the pressure effect.

The pressure influence on the viscosity of pentane has been previously investigated.[47] The viscosities were measured based on the viscosity of pentane at atmospheric pressure. The pronounced logarithmic pressure effect on the viscosity is illustrated in the below graph.

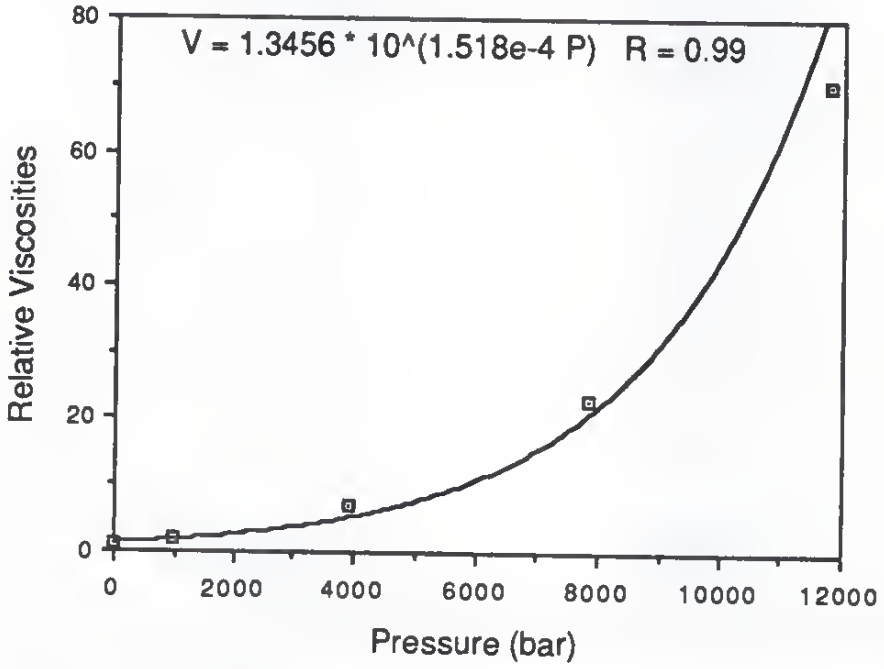


Figure 28. Viscosity Dependence of Pentane with Pressure.

The effect of sheer viscosity on regioselectivity of the reaction between styrene and difluoroallene has been studied within our group.[48] It was found that the regioselectivity does, as expected, vary with changing viscosity.

It is known viscosity alters the reaction outcome. It is known pressure alters viscosity. It would be of interest to discern how much of the pressure influence on reaction outcome is due to viscosity, and how much of it is due to a true pressure effect ($P = P_V + P_T$). Knowing the pressure viscosity relationship, the regioselectivity viscosity relationship, and assuming the true pressure effect (P_T) is negligible, will allow the calculation of the response of regioselectivity to pressure. This calculated relationship can then be compared with the experimentally observed regioselectivity dependance on pressure. If there exists no intrinsic pressure effect ($P_T = 0$) the two relationships will be identical. The difference in the relationships will be indicative of the contribution of a true pressure effect. A plot of the two regioselectivities verses pressure would illustrate the magnitude of the differences. The two lines being equal would indicate all of the pressure effect is attributable to a viscosity effect.

It is quite obvious from Figure 29 that the two lines are not superimposable. There does in fact exist an authentic pressure effect. The calculated regioselectivity appears to have a nonlinear relationship with pressure, whereas the observed regioselectivity shows a distinct linear relationship. Simple viscosity enhancement, while undoubtably influencing the reaction, cannot account for the majority of the observed pressure effects. The altered reaction outcome brought about by the introduction of high pressure originates primarily from a true pressure effect and not viscosity.

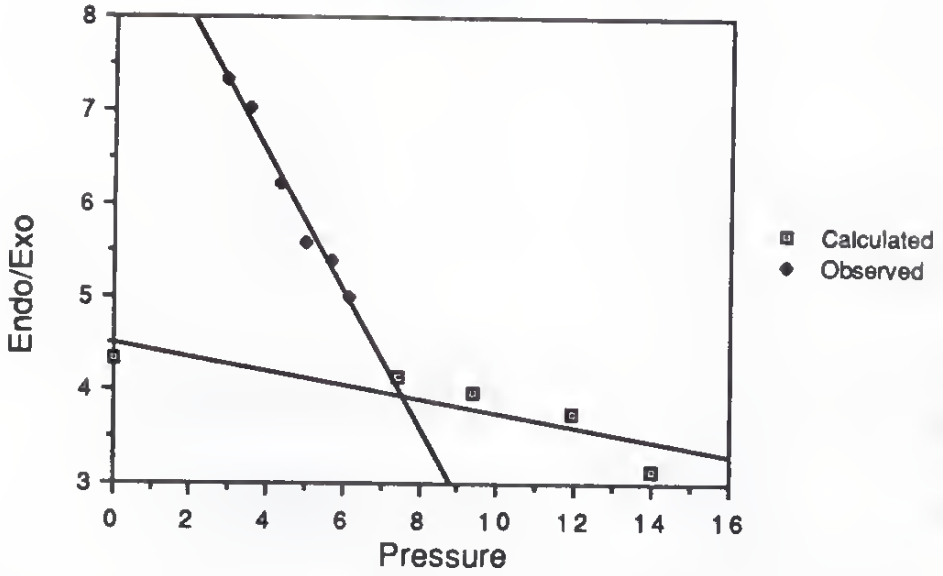


Figure 29. A Graph of the Actual Pressure Regioselectivity and the Calculated Regioselectivity of the Cyclization of Styrene and Difluoroallene.

While the above analysis is useful as a general indicator of the authenticity of a genuine pressure effect, it is not valid in a critical quantitative sense. There are many sources of error associated with the above analysis.

The viscosities determined in the pressure/viscosity relation were determined with the crude dropping of a metal sphere. The viscosities from the regioselectivity study while determined in a more advanced manner, using a Brookfield Viscometer, were nonetheless also sheer viscosities. Sheer viscosity is a bulk solvent property. Of actual interest is the microviscosity, the viscosity in the immediate environment directly surrounding the reacting molecules. There exists no convenient method for the determination

of microviscosity. The relationship between sheer viscosity and microviscosity is not definitively known.

Another source of error is that the pentane pressure-viscosity relationship was determined using an entirely different apparatus and experimental methods than the Seabury pressure work. The degree to which this influences the data cannot be approximated.

In addition to this calculated comparison, comparative experimental cycloaddition reactions were carried out. Difluoroallene was reacted with both neat α-methylstyrene and with an approximate 4 M solution of α-methylstyrene in hexane. The reactions were performed analogously to the deuteriostyrene system and in the manner described in appendix one. The reaction mixture regioselectivities were analyzed over 2 to 11 Kbar. It was found that the reactions carried out in hexane showed an increased but approximately parallel regioselectivity to the reactions carried out neat (Figure 30).

It is evident from Figure 30 that viscosity has an appreciable effect on the cycloaddition reaction. The less viscous reaction mixture, with a hexane solvent, shows a parallel but increased regioselectivity. It is reasonable to expect any comparative reactions between slightly different systems should be valid as long as all reactions are carried out in as similar a manner as possible. Thereby ensuring most of the differences in regioselectivity due to viscosity should be cancelled out, except for any slight differences in viscosity due to the reactants themselves.

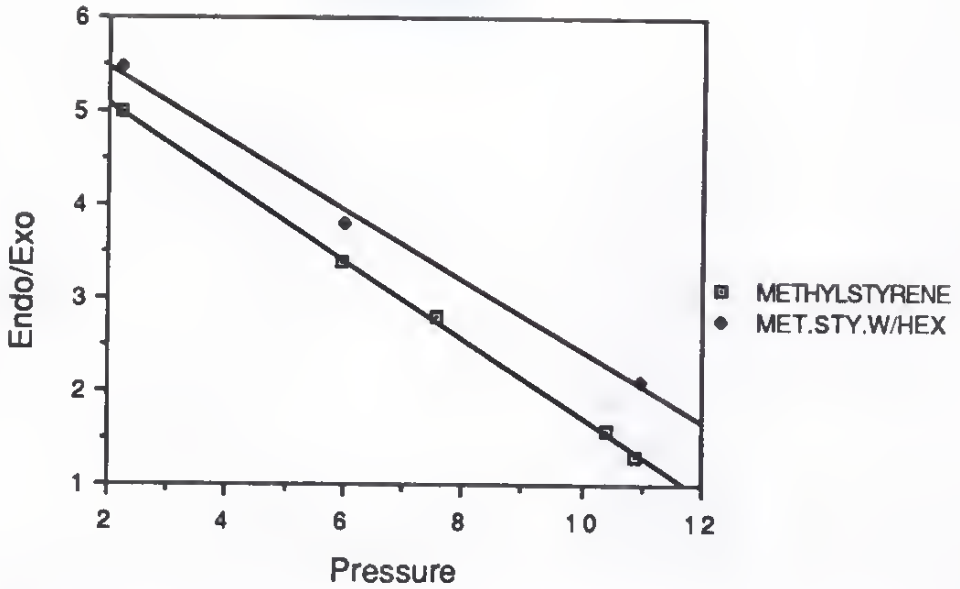


Figure 30. Regioselectivities of the Cycloaddition of Difluoroallene Reacted with α-Methylstyrene Neat, and as a 4M Solution in Hexane.

Conclusion

In conclusion, the imposition of pressure elicits an increase in stereoselectivity and a decrease in regioselectivity in the [2 + 2] cycloaddition of difluoroallene and Z-ß-deuteriostyrene.
This is in strong support of the previously proposed mechanism. Although it is impossible to definitively prove the validity of a mechanism, no other apparent mechanism exists which adequately explains these results in a logical and straight forward manner.

In addition a quantitative measurement of the competition between the two competing paths was ascertained. The difference in volumes of activation between paths A and B is 3.6 cm^3/mol.

The regioselectivity of each competing path was also shown to change with pressure.

Viscosity, while known to be an integrated part of pressure effects, was shown to be not the primary factor responsible for the observed pressure effects.

It is important to note that if the stereoselectivity is not 100%, as assumed, all of the calculated values will be quantitatively skewed but the qualitative interpretation is still valid. Nonetheless this assumption does have a high probability of being valid due to the fact that 95% retention of configuration exists for the exocyclic product at 13 Kbar.

It is also important to note that the total stereorandomization (50 : 50, cis to trans product stereochemistry) from the second intermediate is not guaranteed. Randomization takes place not from the initial intermediate formation but by a subsequent rotation about the C_3-C_4 bond. At high pressures free rotation may not be the case, as a slightly positive volume of activation is associated with almost all[45] gross spatial movements. The degree to which this rotation is impeded cannot be approximated.

CHAPTER THREE
THE HIGH PRESSURE EFFECT ON THE REGIOSELECTIVITY OF THE [2 + 2] CYCLOADDITION REACTION

Introduction

The stereoselectivity of the [2 + 2] cycloaddition of styrene and difluoroallene was thoroughly examined in Chapter 2. The regioselectivity, however, was studied only to a limited extent. It was desired to complete a more in depth study of the steric and thermodynamic factors governing regioselectivity in order to further elucidate the mechanistic details. This can be accomplished by examining the changes in product regiochemisty brought about by the variation of the substituent on the olefin and by the addition of a second olefin substituent.

The addition of another substituent on the olefin is expected to change the steric and thermodynamic characteristics of the molecule. Thermodynamic factors have historically[50] been used to explain the different product outcomes of various olefins in undergoing radical reactions. Steric factors on the other hand have been used to explaining the product distribution from of pressure studies.[51] The comparison of the predicted high pressure effects, from both a thermodynamic and a steric perspective, with the experimental results could potentially be rather enlightening. The comparison would allow the fact of whether a thermodynamic or a steric effect is responsible for determining

the product outcome. This comparison would also allow further insight into the reaction mechanism itself to be gained.

Disubstitution

In order to take advantage of the rather thorough stereochemical knowledge of the styrene system, it was decided styrene would continue to be utilized in the regiochemical study. The methyl group was chosen to be the added second substituent due to its being quite well understood, sterically and thermodynamically, as well as it being readily available.

Methylstyrene and Styrene

Thermodynamic Perspective

The addition of an α-methyl on an olefin undergoing a diradical stepwise cycloaddition, is commonly accepted[52] as being coincident with an increase in stability of the resulting diradical intermediate. An increase in intermediate stability often produces an increase in selectivity of that intermediate.

The addition of a methyl substituent to styrene increases the stability of the diradical and is therefore expected to result in an increase in regioselectivity. Thus α-methylstyrene should show a greater product regioselectivity than the parent styrene.

As this system is subjected to increasing pressures, the reactivities of all intermediates is increased, and a decrease in regioselectivity should result. The change in reactivity of the intermediates brought about by pressure, is expected to be roughly

the same for the disubstituted as the monosubstituted cases. Thus the decrease in regioselectivity with increasing pressure should be roughly the same for α-methylstyrene as for styrene. The overall thermodynamic prediction follows that the α-methylstyrene should be more regioselective than styrene, and that both systems are expected to undergo similar changes in regioselectivity with respect to pressure. The difference in regioselectivities of the two systems should be indicative of the added stability of the disubstituted intermediate.

Steric Perspective

Pressure effects originate from the changes in volumes which occur when a molecule proceeds from a stable reactant to a transition state. Steric effects change the effect of pressure not by increasing the volume of the molecule itself, but by changing the volume difference between starting material and transition state. An increase in pressure favors the path with the greatest negative change in volume. As one path is favored over another it's regiochemical contribution to the overall product mixture will concurrently be enhanced.

The two possible cyclization paths (A and B, Figure 25) posses different volumes of activation as well as different regioselectivities. One can make predictions on how the addition of a α-methyl group will affect the volumes of activation of the competing paths, and by comparison of these predictions with the actual product regiochemistries, the validity of these predictions

can be tested. This change in volume of activation brought about by the addition of a methyl group will be predicted, along with how this volume change is expected to effect the path differentiation and product regioselectivity.

The separation between paths originates from the first intermediate rotating to the second intermediate instead of cyclizing to product. The impetus for rotation about the C_3-C_4 bond of the initial intermediate to the second intermediate is a reduction of steric interaction between the phenyl substituent and the C_3 hydrogen. The addition of an α-methyl substituent on the olefin increases the steric constraint of this initial intermediate due to the added steric interaction of the methyl group with the C_3 hydrogens. In the monosubstituted styrene case, rotation about the C_3-C_4 bond greatly reduces unfavored steric interaction between the phenyl and hydrogens (see Figure 24). The disubstituted case is not so straight forward. Rotation about the C_3-C_4 bond decreases the steric interaction of the phenyl substituent but the methyl group is then forced to rotate directly into a highly sterically congested area (figure 31). It is therefore expected that the methylstyrene intermediate will be <u>less</u> likely than the styrene intermediate to undergo C_3-C_4 bond rotation (path B). Cycloaddition of α-methylstyrene is predicted to proceed primarily by path A and is therefore expected to posses <u>lower</u> regioselectivity than the styrene system. This is in direct contrast to the predictions based on thermodynamic control.

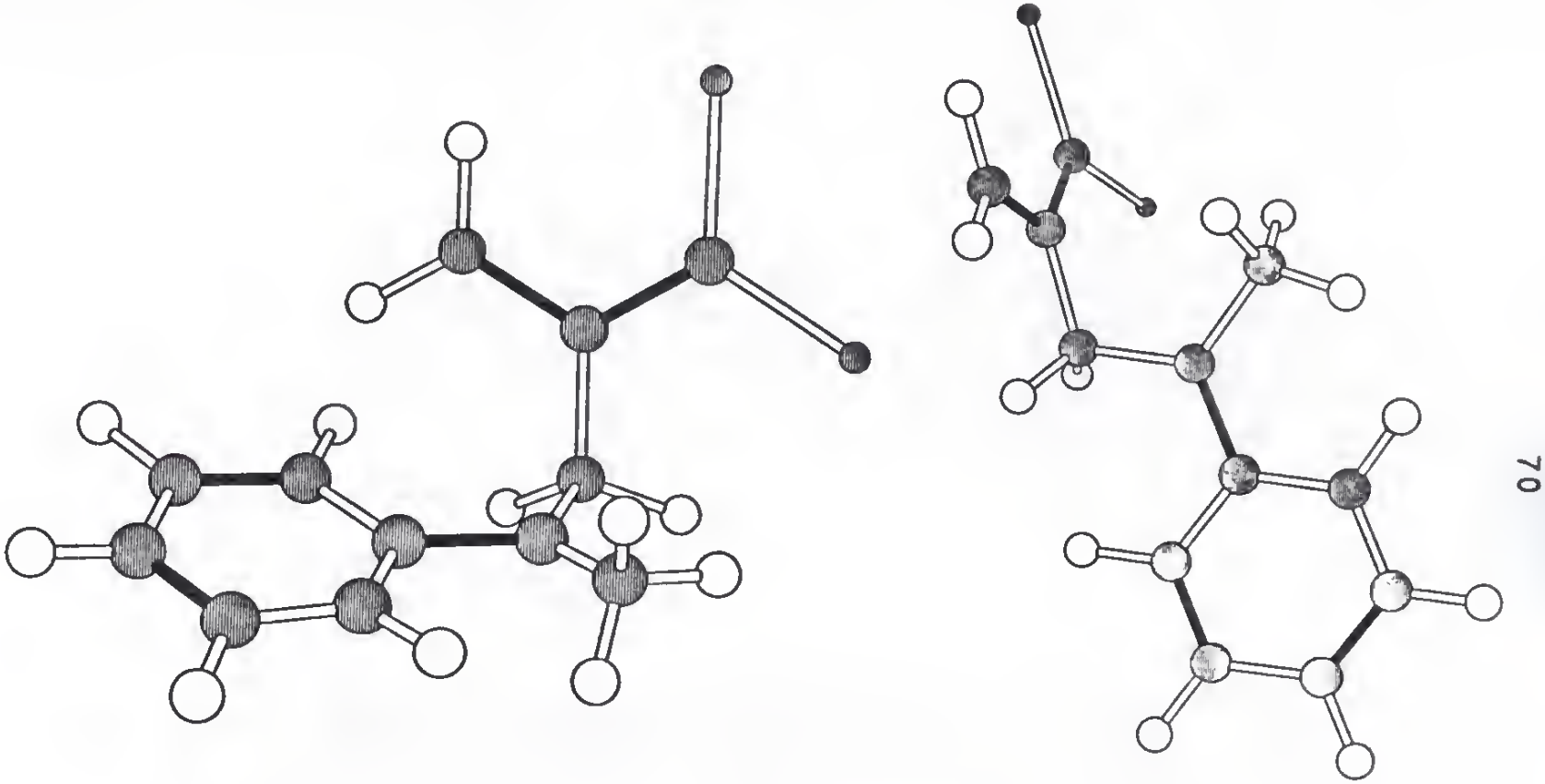


Figure 31. Initial and Second Intermediate from the [2 + 2] Cycloaddition of Methylstyrene and Difluoroallene.

In summation, if the system is under thermodynamic control methylstyrene will show a marked increase in regioselectivity with respect to styrene. If the system is under steric control methylstyrene will show a marked decrease in regioselectivity with respect to styrene.

Results and Discussion

Difluoroallene was condensed into low density polyethylene tubes, as discussed in appendix B, containing a weighed amount either styrene or methylstyrene and a few milligrams of hydroquinone inhibitor. The tubes were sealed and subjected to various pressures. The regiochemistries of the products were analyzed by using either quantitative 300 MHz ^{19}F NMR, or by a minimum of 4 correlating injections on a F.I.D./G.C.

Table 7. The Regioselectivity of Styrene and Methylstyrene at Various Pressures.

	Pressure (Kbar)	Regioselectivity Endo : Exo
Methyl Styrene	2.20	83.3 : 17.7
	5.99	77.2 : 22.8
	10.40	61.2 : 38.8
	10.87	56.7 : 43.3
Styrene	1.89	86.1 : 14.0
	4.10	84.1 : 15.9
	5.99	82.0 : 18.0
	8.03	77.4 : 22.6
	11.03	70.6 : 29.4

The product regiochemical ratios indicate that methylstyrene is less regioselective than styrene. This is in direct opposition to the predictions based on thermodynamic considerations. Thus the predominate influential factor in determining regioselectivities within this system is steric in nature. The magnitude of the difference in regioselectivity can be illustrated by graphing the two regioselectivities against pressure.

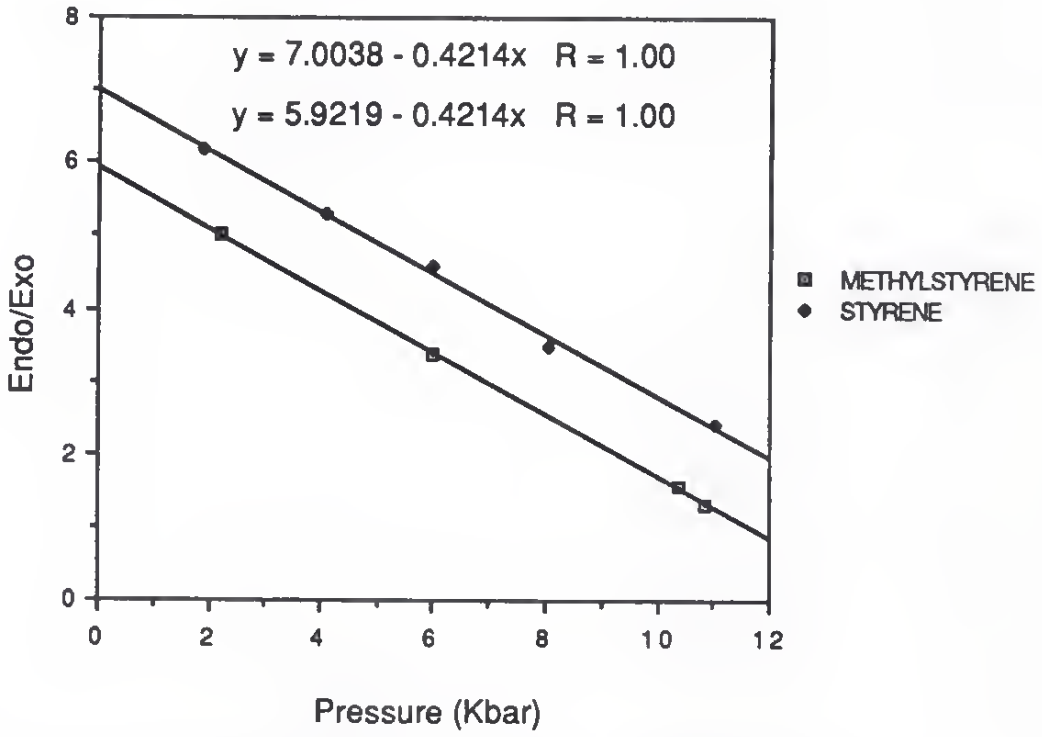


Figure 32. Pressure Dependence on the Regioselectivity of the Cyclization of Methylstyrene and Styrene with Difluoroallene.

The slopes of the two lines are remarkably equal, with methylstyrene being significantly less regioselective than styrene. This was not particularly anticipated. If the individual paths have

the same regioselectivity in both systems, the offset of the two lines is proportional to the difference in volumes of activation. The fact that the two lines are parallel can be rationalized by the fact that these two systems are very similar and are being subjected to the same imposed conditions.

It was desired to study an additional system to verify our findings and to broaden our knowledge of the cycloaddition mechanism outside of the styrene system. It was also desired to further probe the comparative changes an added methyl group imparts on the system.

Methylacrylonitrile and Acrylonitrile

Superficially it may be expected very similar trends will exist for the acrylonitrile system as for the styrene system. Both systems are conjugated radical stabilizing groups and both are perturbed in the same fashion by adding the same methyl substituent.

Thermodynamic Perspective

Thermodynamic considerations predict the same reaction outcome for an added α-methyl substituent in the acrylonitrile case as the styrene case. The added substituent should in both cases increase the stability of the disubstituted olefin, and result in an increase in regioselectivity. Methylacrylonitrile should then be more stable than acrylonitrile, and display a difference in regioselectivity similar to that which was observed in the styrene system.

Steric Perspective

Superficially the predicted steric perturbations can be seen as being the same as those of the methylstyrene-styrene system. One α-methyl group has been added in both cases. Upon further reflection significant differences come to light.

The styrene system has an inherent steric driving force inducing the system to undergo rotation about the C_3-C_4 bond, and proceed via path B to the second intermediate. This driving force is an alleviation of 1,5 steric interaction between the phenyl and the hydrogen. The cyano group on the other hand, with a linear geometry has virtually no C_3 hydrogen steric hindrance and thus acrylonitrile possesses no driving force to proceed by pathway B (figure 33). It is then predicted that at ambient pressure cyclization of acrylonitrile will proceed predominantly by pathway A.

In the disubstituted case, the imposition of a methyl group on acrylonitrile will introduce steric constraints between itself and the adjacent C_3 hydrogens. In the case of methylstyrene the greatest steric constraint exists between the phenyl group, and the C_3 hydrogens. In contrast, the bulkiest group in methylacrylonitrile (Figure 34) is not the cyano but is instead the methyl! Thus the steric driving force for the rotation about the C_3-C_4 bond in methylacrylonitrile emanates from the methyl group. The methylacrylonitrile is predicted to undergo cyclization via a modified path B, where the methyl group, not the cyano group rotates down, out of the plane of the molecule. Regardless of the downward rotating group, the second intermediate will be more stable and

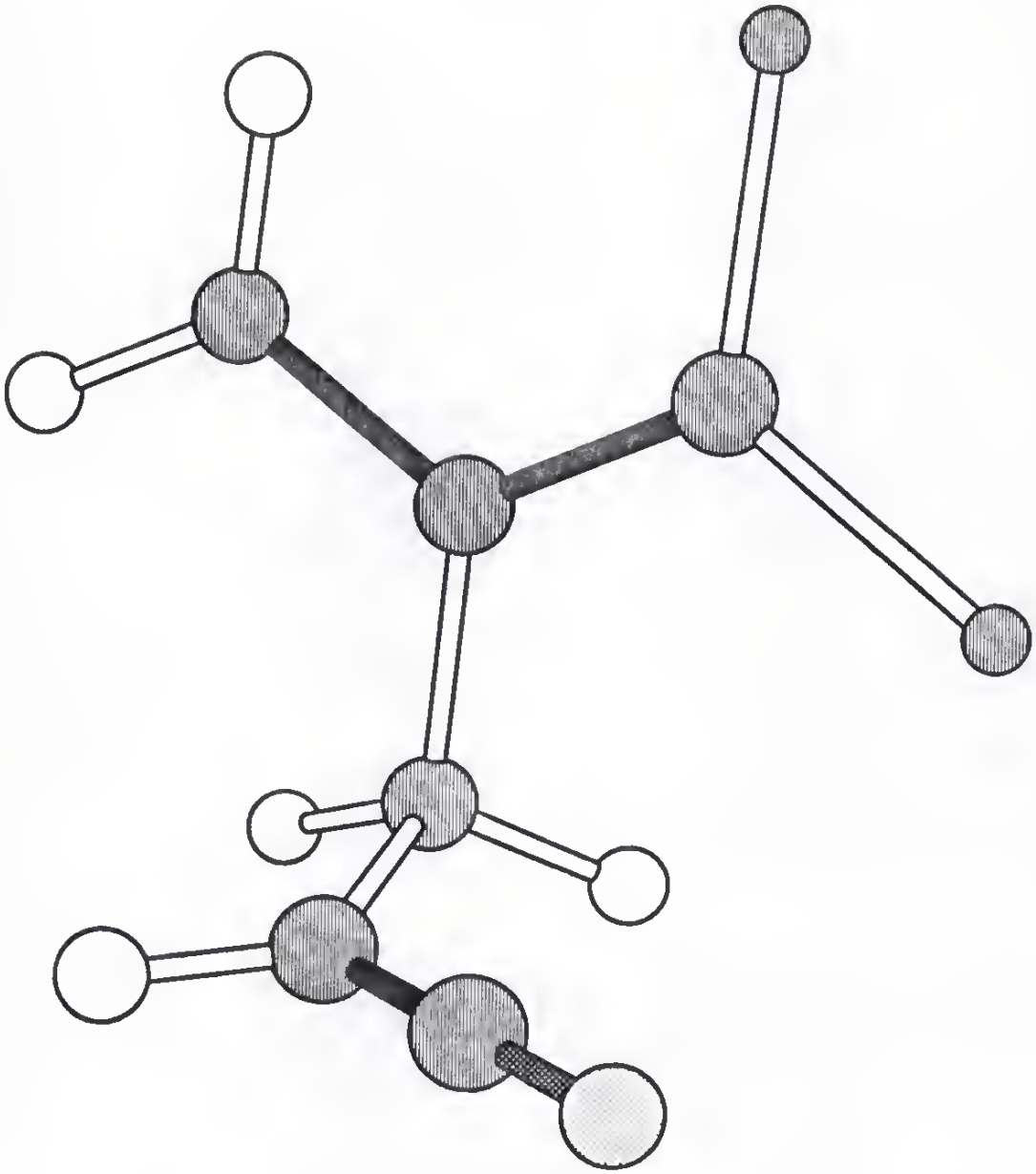


Figure 33. Initial Intermediate from the [2 + 2] Cycloaddition of Acrylonitrile and Difluoroallene.

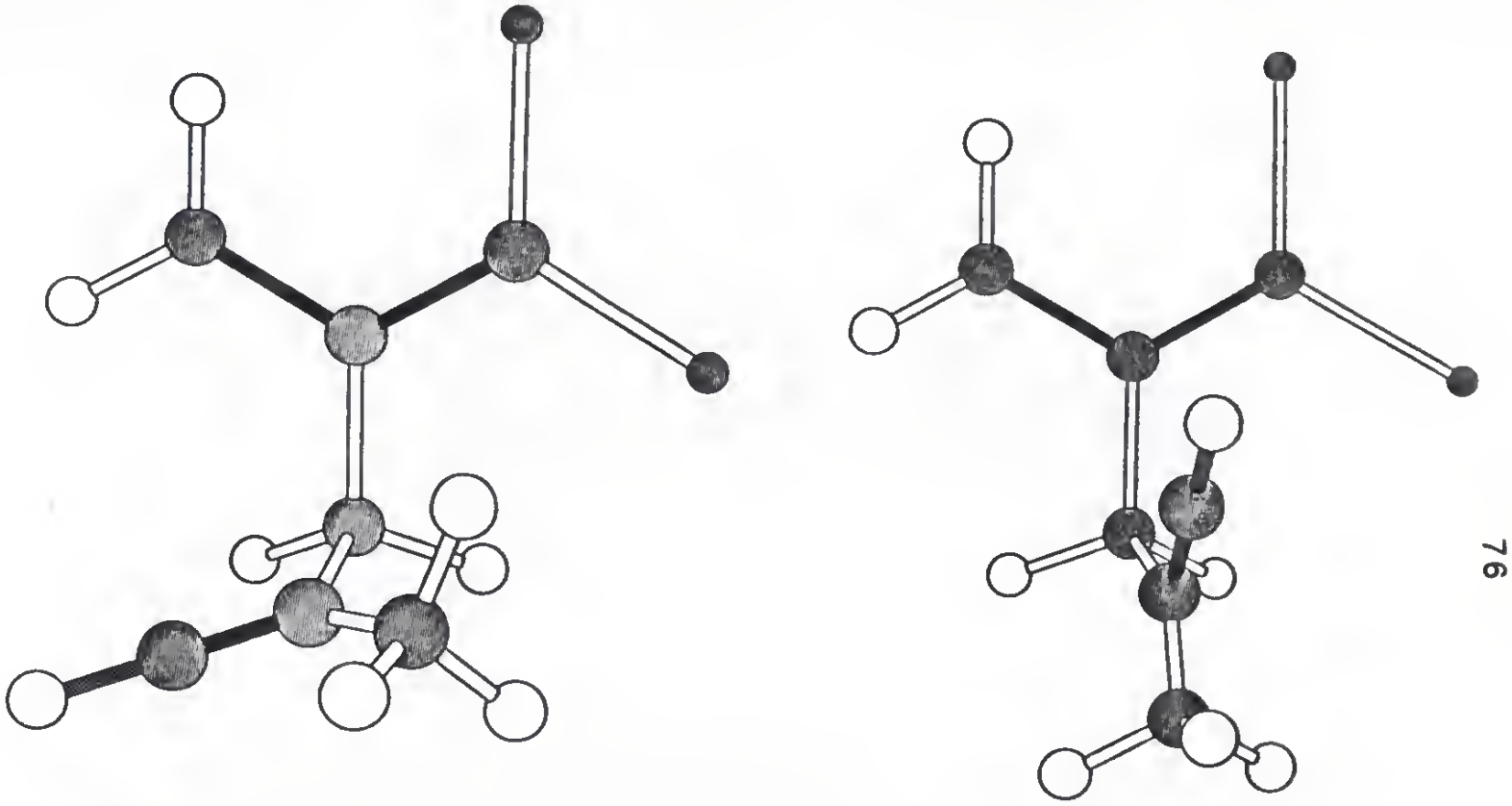


Figure 34. Initial and Second Intermediate from the [2 + 2] Cycloaddition of Methylacrylonitrile and Difluoroallene.

more selective in cyclization than the initial intermediate. Due to the added methyl steric driving force, methylacrylonitrile is expected to undergo cyclization via the second intermediate to a much larger extent than in the case of the unsubstituted acrylonitrile. Because path B has a larger degree of regioselectivity, methylacrylonitrile should posses a significant regioselectivity when cyclizing with difluoroallene. The expected steric scenario is then for unsubstituted acrylonitrile to proceed predominantly by path A and exhibit quite little regioselectivity.

Results and Discussion

Methylacrylonitrile and acrylonitrile were studied in the same fashion as the styrene systems. Reactions were carried out without solvent in polyethylene tubes at various pressures. The regiochemical composition of product mixtures were determined using quantitative 300MHz ^{19}F NMR.

Table 8. Regioselectivities at Various Pressures of the Cyclization of Difluoroallene and Acrylonitrile and Methylacrylonitrile.

	Pressure (Kbar)	Regioselectivity Endo : Exo
Acrylo-nitrile	2.36	74.5 : 25.5
	5.99	67.5 : 32.5
	10.87	57.6 : 42.4
Methyl-acrylo-nitrile	2.05	89.5 : 10.5
	5.67	87.3 : 12.7
	11.03	73.7 : 26.3

The methylacrylonitrile is more regioselective than acrylonitrile. This was expected for both thermodynamic and steric control. The changes in regioselectivity of acrylonitrile and methylacrylonitrile over the pressure range studied are quite similar. A 16.9% reduction of the endo isomer occurs in the acrylonitrile system, where a 15.8% reduction occurs for methylacrylonitrile. This similar change suggests similar processes are occurring in both systems. The absolute regioselectivity of both systems can be seen by a plot of regioselectivity verses pressure.

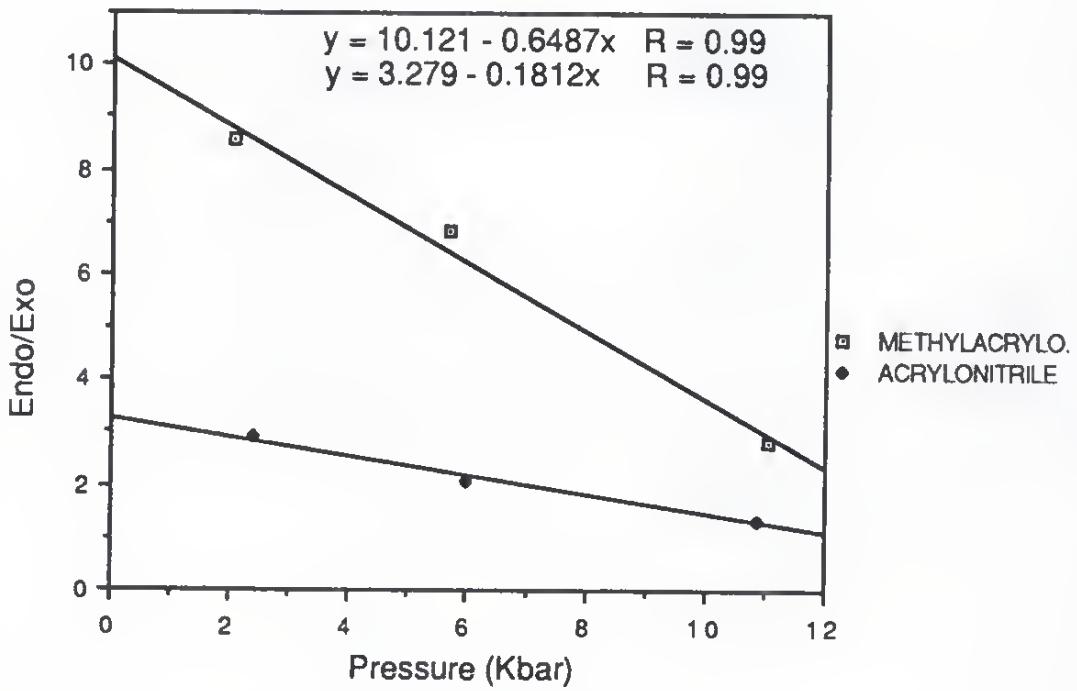


Figure 35. Pressure verses Regioselectivity of the Cylization of Methylacrylonitrile and Acrylonitrile with Difluoroallene.

These two lines are unambiguously not parallel. Acrylonitrile shows a very low regioselectivity. Methylacrylonitrile, on the other hand shows a significant regioselectivity and an appreciable pressure dependence on that regioselectivity. The substantial lessening of regioselectivity in acrylonitrile and methylacrylonitrile with pressure agree remarkably well with the predictions made based on steric control governing the outcome of the reaction.

Butadiene

It was desired to investigate the regioselectivity of other systems. Butadiene was chosen to be studied. In theory, the [2 + 2] cycloaddition of butadiene and difluoroallene should occur quite readily due to the very stable diradical intermediate which results from initial bond formation.

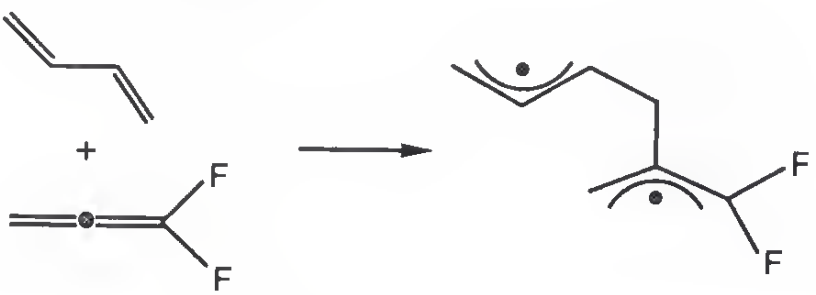


Figure 36. Diradical Intermediate for the [2 + 2] Cycloaddition of Butadiene and Difluoroallene.

It has been shown[42] that at ambient pressures, butadiene and difluoroallene react predominantly in a [2 + 4] manner. Only small

amounts of the [2 + 2] endocyclic product are evident. None of the exocyclic regioisomer can be detected. It was initially expected that as the pressure was increased the rate of the [2 + 2] cycloaddition would be enhanced along with a decrease in regioselectivity. Thus, with increasing pressure, the amount of [2 + 2] product should be increased and the relative amount of the exocyclic isomer should be raised.

Butadiene and difluoroallene were condensed into reaction tubes containing hexane and hydoquinone following the same method described in appendix two. The reaction mixtures were analyzed by quantitative ^{19}F NMR.

The [2 + 4] Diels-Alder adduct was the overwhelming product. At low pressures (2.2 Kbar) the ratio of [2 + 2] to [2 + 4] cycloaddition products was 1 : 10.3 (8.82 % [2 + 2]). At 11 Kbar only traces of the [2 + 2] endocyclic product could be observed. The ratio of [2 + 2] to [2 + 4] cycloaddition products dropped to 1 : 54.2 (1.81 % [2 + 2]). In no instance could the exocyclic difluoromethylene product be detected.

In retrospect, this should have been expected. The [2 + 2] and [2 + 4] cycloaddition reactions both have negative volumes of activation, but the concerted [2 + 4] process is expected[44,52] to be significantly more negative than the stepwise [2 + 2]. As pressure is increased, the rate of the reactions are increased in proportion to their volumes of activation. As the pressure is increased, the [2 + 2] cycloaddition is enhanced but the [2 + 4] is enhanced to a greater

degree. Thus the percent of Diels-Alder products will be increased with pressure. An increase in the ratio of exocyclic to endocyclic [2 + 2] products has assuredly accompanied the increase in pressure, but because of the overwhelming presence of the [2 + 4] reaction, the exocyclic [2 + 2] product could not be detected. It is interesting to note that the butadiene reactions were one of the few reactions which consumed all of the difluoroallene without resulting in a significant amount of oligomers being formed. This is explained by the ease in which the [2 + 4] reaction occurs, and it also illustrates the relative inadequacy of [2 + 2] cycloadditions.

Conclusion

An addition of an α-methyl substituent brings about drastic changes in the regioselectivity of the [2 + 2] cycloaddition of an olefin and difluoroallene. Thermodynamics and steric effects predict directly contrasting regioselectivities for the cyclizations.

Historically thermodynamic stabilities have commonly been used to predict product distribution. Thermodynamics predicts that both methylstyrene and methylacrylonitrile will show an enhanced regioselectivity when compared to the unmethylated analogs. These thermodynamic predictions are not realized. In fact an entirely different regioselectivity is observed.

Steric and volume considerations correctly predict methylstyrene will be less regioselective than styrene. It also correctly predicts acrylonitrile will posses relatively low regioselectivity.

It is interesting to note that although quantitative studies were not performed, a distinct thermodynamic control over the [2 + 2] cycloaddition reaction can be ruled out. Steric factors and not thermodynamics exert the predominate influence governing the partitioning between pathways.

CHAPTER FOUR
EXPERIMENTAL

General Methods

Nuclear magnetic resonance (NMR) chemical shifts are reported in parts per million (ppm) downfield (δ) from internal reference TMS for ^{1}H, and upfield (φ) from internal reference $CFCl_3$ for ^{19}F. All NMR spectra were obtained on either a Varian VXR-300 or a General Electric QE-300 instrument.

Quantitative gas chromatography was performed on a Hewlett-Packard 5710A equipped with a flame ionization detector and a HP 3380S Integrator. Preparative gas chromatography was performed on a Varian Aerograph A90-P3 having a thermal conductivity detector.

The product ratios were determined either by a minimum of four corroborating injections on a HP 5710A gas chromatograph or by ^{1}H or ^{19}F quantitative NMR.

All high pressure reactions were performed on the same double-walled piston cylinder type pressure reactor. A thorough discussion of the high pressure equipment and general procedure used in these reactions can be found in Appendix B.

Materials

Difluoroallene Synthesis

This synthesis is essentially the same as that performed by Dolbier, Burkholder, and Piedrahita.[53] Detailed spectral data can be found within this reference.

1,2-Dibromo-3,3,3-trifluoropropane. A 500 ml three necked flask was equipped with a sintered glass gas inlet tube, a magnetic stir bar, and a large dry ice condenser. The flask was cooled to 0° C and illuminated with a sun lamp. Approximately 150 ml(2.93 mol) of bromine was added, and 100 ml(1.04 mol) of 1,1,1-trifluoropropene (P.C.R.) was slowly bubbled through the bromine for approximately 2.5 hours. During this time the bromine solution turned a dark apricot color. The excess bromine was distilled off. The desired 1,2-dibromo-3,3,3-trifluoropropene was distilled out of the reaction mixture, and redistilled over 110-120° C to give 186 grams of material for a 73% isolated yield. ^{1}H NMR δ4.8(m,1H), 4.2(m,2 H),^{19}F NMR φ 71.0 (d).

2-Bromo-3,3,3-trifluoropropene. A 250 ml three-necked flask was fitted with a pressure equalizing addition funnel, a stopper, and a short vigreux column to which was connected in series a 0° C trap, a -78° C trap, a heavy oil bubbler, and a drying tube. Solid KOH, 140 grams (2.5 mol) was added to the flask and 94.1 grams (0.365 mol) of 1,2-dibromo-3,3,3-trifluoropropane was added to the addition funnel. The three necked flask was cooled to 0° C and the reactant was slowly dropped onto the KOH. Upon completion of reactant addition, the temperature of the flask was slowly raised to 110° C

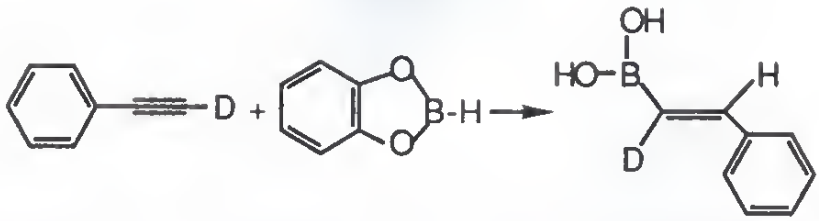
over 3 hours. The desired 2-bromo-3,3,3-trifluoropropene (55.9 grams) was retrieved from the cold traps for an 83.4% isolated yield. ^{1}H NMR δ6.08(1H), 6.52(1 H), ^{19}F NMR φ(67.0).

1,1-Difluoroallene(6). All glassware was baked in drying oven for twenty four hours and assembled under nitrogen atmosphere. A 1,000 ml three-necked flask was fitted with a pressure equalizing addition funnel, a mechanical stirrer, and a Friedrichs condenser to which was connected in series two -78° C spiral traps, a heavy oil bubbler, and a drying tube. The reaction flask was charged with 44.8 grams (0.256 mol) of 2-bromo-3,3,3-trifluoropropene (stored over $CaCl_2$) and 250 ml of hexane which had been freshly distilled twice from $LiAlH_4$. The reaction flask was cooled to below -90° C with a hexane liquid nitrogen slush. n-Butyl lithium (121 ml, 0.303 mol) was transferred by cannula into the addition funnel and slowly added over 2.5 hours. After butyl lithium addition was complete the reaction was allowed to let stir for an additional hour. The reaction flask was never permitted to rise above -90° C. Liquid nitrogen addition to the slush bath was then ceased and the temperature was allowed to reach room temperature over several hours. The flask was then heated to hexane reflux for one hour. The difluoroallene (16.57 grams) was collected in the spiral cold traps. Difluoroallene must be stored at dry ice temperature to prevent decomposition. A 80.9 % yield was obtained. ^{1}H NMR ,δ6.06(t), ^{19}F NMR φ105.9 Figure 37, Appendix A.

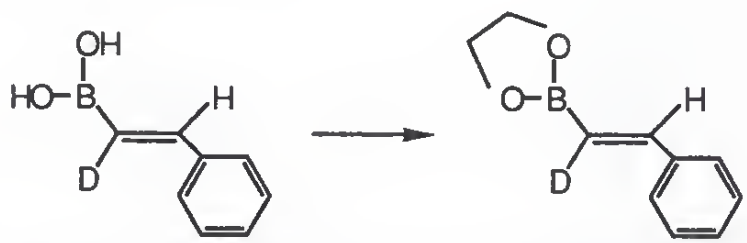
Z-ß-Deuteriostyrene Synthesis

The synthesis is essentially that as performed by Dolbier and Wicks.[42]

Deuteriophenylacetylene. A dried 1000 ml three-necked flask was equipped with a mechanical stirrer, a dry ice condenser, and a pressure equalizing addition funnel. Into the flask was placed 24.3 grams (1.0 mol) magnesium turnings and 300 ml of anhydrous diethylether.The addition funnel was filled with 90.2 grams (0.835 mol) of bromoethane which was added to the reaction mixture over 2 hours under a nitrogen blanket and with vigorous stirring.After the addition of bromoethane was complete the mixture was allowed to stir an additional hour. Freshly distilled phenylacetylene (24.10 grams, 236 mol) was placed in the addition funnel and added dropwise over one hour. This mixture was allowed to stir for 3 hours. Deuterium oxide (33.0 grams (1.65 mol) having 99.8% purity) was slowly added over 1.5 hour. White vapor was readily apparent during the D_2O addition. The solution was allowed to stir for an additional 2 hours. All solid was removed with filtration and the solution was dried overnight with $MgSO_4$. Deuteriophenylacetylene (17.03 grams) was isolated by distillation for a 70.0% isolated yield. ^1H NMR shows a greater than 99.9% deuteration incorporation by integration of the aromatic protons with the acetylenic proton. ^1H NMR δ 7.38 (m, 5H), 3.06 (s, 1H).

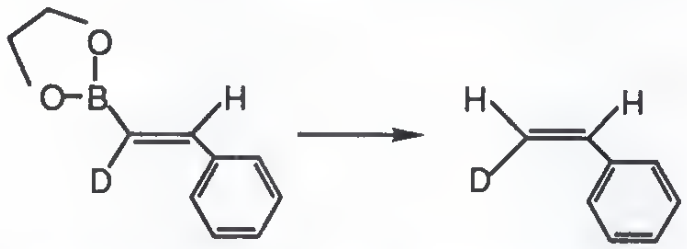


α-Deuterio-ß-Phenylethenylboronic Acid. All glassware was dried overnight in a drying oven. A 100 ml three necked flask was fitted with a mechanical stirrer, a pressure equalizing addition funnel, and a West condenser. Catecholborane (Aldrich, 49.53 grams, 0.428 mol) and deuterophenylacetylene (39.54 gram, 0.384 mol) were anhydrously transferred to the flask and addition funnel respectfully. The reaction flask was cooled to 0º C, and the phenlyacetylene was added over a 10 minute time period. The mixture was allowed to stir at 0º C for 15 minutes and for an additional hour at room temperature. The reaction was then heated to 70º C and stirred for and additional two hours. Deionized water (200 ml) was added and stirring continued at 85º for 3 hours. Stirring was ceased and the reaction mixture was allowed to cool. Crystals of α-deuterio-ß-phenylethenylboronic acid(29.68 gram, 0.199 mol) were collected and recrystalized from water for a 34.6% isolated yield. M.P. 162-164º C.



2-((Z)-α-Deuterio-ß-Phenyl)ethyl-1,2-Dioxaborolane. A dry 500 ml single necked round bottom was fitted with a magnetic stir

bar, a Dean-Stark trap, and a Graham condenser which was topped with a drying tower. Into this flask was placed α-deuterio-ß-phenylethenylboronic acid (29.68 gram, 0.199 mol), ethylene glycol (12.5 gram, 0.225mol), and 200 ml of toluene. This mixture was heated to reflux with stirring for 50 hours. The resultant brown oil was crystalized by refrigeration and recrystalized from hexane to yield 2-((Z)-α-deuterio-ß-phenyl)ethyl-1,2-dioxaborolane(21.09 gram, 0.121 mol) in a 60.2% isolated yield. M.P. 44-45° C.



Z-ß-Deuteriostyrene (7). A dried three necked flask was equipped with a pressure equalizing addition funnel, a magnetic stir bar, and a West condenser. Into the flask was placed boric ester (21.0 gram, 0.120 mol,vacuum dried), 4-t-butylcatechol inhibitor (≈0.05 grams). Freshly distilled acetic acid (70 ml). was placed in the addition funnel and added over 15 minutes to the vigorously stirred reaction mixture. The solution was then heated to 120° C for 10 minutes, the heat was then reduced to 90° C and the reaction mixture was allowed to stir for an additional 1.5 hours. The solution was then poured onto ice, extracted with pentane, and neutralized with base. The pentane was rotoevaporated off to isolate Z-ß-deuteriostyrene (6.90 gram, 0.0657 mol) in greater than 99.9%

isotopic purity for a 56% isolated yield. ^{1}H NMR δ 7.30 (m, 5H), 6.68(1H, dt), 5.69(0 H), 5.2 (d, 1H), Figure 38, Appendix A.

A 12.0% overall yield was obtained starting from phenylacetylene.

Olefins

The methylstyrene (Aldrich), styrene (Fisher), methylacrylonitrile (Aldrich), and acrylonitrile (Kodak) were distilled once before using.

Reaction Methods

General Method

The apparatus and sealing of reaction tubes is described in appendix B. The reactant olefin is weighed into the reaction tube containing hydroquinone inhibitor. The difluoroallene is measured and condensed into the reaction tube using standard vacuum line techniques. Large olefin to difluoroallene ratios (7 to 1) are used to prevent excessive difluoroallene oligomerization. The top of the tube was then sealed and the reaction tube is then subjected to the desired high pressure in the manner described in Appendix B. The reaction was allowed to proceed at the elevated pressure for 0.5 to greater than 100 hours. The very high pressure runs are carried out for short periods of time in order to limit the degree of difluoroallene dimerization. Most of the very high pressure runs were not allowed to proceed to completion because the time necessary for this to occur would permit too much interfering

oligomerization products to also form. Upon completion of the high pressure run, the sample tube is removed from the apparatus and analyzed.

The specific analysis methods used for each system and distinct NMR peaks are listed below. A representative NMR spectrum of each system can be found in Figures 39 through 43 of Appendix A. Detailed spectral data can be found in the references cited within. A composite table of all [2 + 2] cycloaddition reaction pressures, reaction times, product ratios, and overall yields can be found at the end of this chapter (Table 9). All yields except for the deuteriostyrene system, were determined by N.M.R. integration of product peaks against the internal standard, fluorobenzene. Yields for the deuteriostyrene system were determined in an approximate manner by mass balance of G.C. integrations.

Deuteriostyrene System

The regiochemical isomer ratio is determined from a minimum of four correlating injections on a Hewlett-Packard 5709 gas chromatograph (FID) using a 10 foot 20% QF-1 column. The detector and injector temperature was 200° C, the column temperature was 130° C, and the nitrogen pressure was 100 p.s.i. The desired [2 + 2] cycloaddition reaction products have elution times as follows; 2,2-difluoro-3-phenyl-1-methylenecyclobutane (8, the endocyclic isomer) 11.2 minutes, and 3-phenyl-1-(difluoromethylene)cyclobutane (9, the exocyclic isomer) 8.1 minutes. Other prevalent peaks consist of primarily the oligomers of

of difluoroallene. Their elution times are as follows; 3-(difluoromethylene)-7,7,8,8-tetrafluorobicyclo[4.2.0] oct-1(6)-ene, a difluoroallene trimer, which elutes at 6.1 minutes, 7-(difluoromethylene)-2-methylene-1,1,5,5-tetrafluorospiro [3.3]heptane, a spiro trimer of difluoroallene, elutes at 3.9 minutes, 1-(difluoromethylene)-2-methylene-3,3-difluorocyclobutane, a difluoroallene dimer, elutes at 3.3 minutes, and unreacted styrene elutes at 1.9 minutes.

The absolute retention times varied somewhat depending on the pressure at which the reaction was carried out because of the differing degrees of styrene dimer present in the reaction mixture. The higher pressure reaction mixtures were noticeably more viscous than the lower pressure mixtures. The higher pressure elution times are slightly longer than low pressure elution times but the characteristic elution pattern remained unchanged.

After the regiochemical isomer ratios were determined, the individual regioisomers were separated using a Varian Aerograph 90-P preparative G.C. with an attached thermalconductivity detector. The column used was a 10' X 1/4" 20% QF-1 at 120°C. A typical injection size was 100 µl with an attenuation of 128. The injector and detector temperatures were 200° C. The flow rate was 50 cm^3/min. The elution times are as follows; 2,2-difluoro-3-phenyl-1-methylenecyclobutane 26.0 minutes, and 3-phenyl-1-(difluoromethylene)cyclobutane 18.6 minutes. The other prevalent peaks elute at the following times; 3-(difluoromethylene)-7,7,8,8-tetrafluorobicyclo[4.2.0] oct-1(6)-ene, a difluoroallene trimer,

14.0 minutes, 7-(difluoromethylene)-2-methylene-1,1,5,5-tetrafluorospiro [3.3]heptane, a difluoroallene spiro trimer, 8.8 minutes, 1-(difluoromethylene)-2-methylene-3,3-difluorocyclobutane,a difluoroallene dimer, 7.6 minutes, and unreacted styrene 5.0 minutes.

The stereochemistry of the individual regioisomers were then analyzed using ^1H NMR (300 MHz). The T_1 relaxation times of all endocyclic protons were determined. The endocyclic difluoromethylene isomer (2,2-difluoro-3-phenyl-1-methylenecyclobutane) has a proton cis to the phenyl group with a 3.1 second relaxation time and a trans proton with 5.6 second relaxation time. The exocyclic difluoromethylene isomer (3-phenyl-1-(difluoromethylene)cyclobutane) has a proton cis to the phenyl group with a 3.3 second relaxation time and a trans proton with a 3.6 second time. All NMR experiments were performed with a delay of 28 and 18 seconds respectively, in order to ensure that all protons were fully relaxed before the next pulse to ensure a quantitative integration was obtained The standard number of transients accumulated was 64, a minimum of 48 transients were taken for concentrated samples, and a maximum of 128 transients was acquired for dilute samples. Transients were continued to be acquired until good baseline separation occurred between stereoisomeric protons.

4-Deuterio-2,2-difluoro-3-phenyl-1-methylenecyclobutane(8). The proton cis to the phenyl group appears at 2.90 ppm as a doublet

4-Deuterio-2,2-difluoro-3-phenyl-1-methylenecyclobutane(8). The proton cis to the phenyl group appears at 2.90 ppm as a doublet (J_{HF}=10.1 hz). The proton trans to the phenyl group appear at 2.77 ppm as a doublet (J = 8.0). Figure 39, Appendix A.

2-Deuterio-3-phenyl-1-(difluoromethylene)cyclobutane(9). The cyclobutane protons cis to the phenyl group appear at 3.11 ppm as a multiplet. The protons trans to the phenyl group appear at 2.82 ppm in a complex multiplet pattern. Figure 40, Appendix A.

Acrylonitrile System

Approximately 0.4 ml of acrylonitrile was used in each reaction along with enough difluoroallene for an approximate 7 to 1 mole ratio. Once the reaction tube was removed from the high pressure apparatus, the regioisomer ratio of the reaction mixture was determined by quantitative ^{19}F NMR (Figure 41). The relaxation times of all fluorines were determined and a delay of 25 seconds was used for all pulse sequences. A minimum of 112 transients was accumulated for all reaction runs.

Oligomers.[23] In all cases dimers and trimers of difluoroallene have been present. The most prominent oligomers are as follows; 3-(difluoromethylene)-7,7,8,8-tetrafluorobicyclo[4.2.0] oct-1(6)-ene, a difluoroallene trimer φ 90.7 (d of p, 1F, J_{FF}=50.3 and J_{HF}=1.7 Hz), φ 94.4 (d of p, 1F, J_{FF}=50.3 and J_{HF}=1.7 Hz), φ1123.7 (m, 2F); a spiro trimer of difluoroallene, 7-(difluoromethylene)-2-methylene-1,1,5,5-tetrafluorospiro [3.3]heptane, φ 80.0 (dd, 1F, J_{FF} =31.0 and

Endocyclic isomer: 2,2-difluoro--3-methylenecyclobutanecarbonitrile.[54] ^{19}F NMR φ 91.68(complex d,1F), 98.71(complex d, 1F).

Exocyclic isomer: 1-methyl-3-(difluoromethylene)cyclobutanecarbonitrile.[4] ^{19}F NMR φ 95.0(virtual s, 2F).

α-Methylacrylonitrile System

Approximately 0.4 ml of α-methylacrylonitrile was used in each reaction. The mole ratio of olefin to allene was approximately 7 to 1. Once the reaction tube was removed from the high pressure apparatus, the regioisomer ratio of the reaction mixture was determined by quantitative 19F NMR (Figure 42). The relaxation times of all fluorines were determined and a delay of 25 seconds was used for all pulse sequences. A minimum of 144 transients was accumulated for all reaction runs.

Enodcyclic isomer: 2,2-difluoro-1-methyl-3-methylenecyclobutanecarbonitrile.[3] ^{19}F NMR φ 97.9 (d, 1 F, J_{FF} =206.4), φ 105.5 (d, 1F, J_{FF} =206.4).

Exocyclic Isomer: 1-Methyl-3-(difluoromethylene)cyclobutnecarbonitrile.[3] ^{19}F NMR φ 94.0,(pent, J=3.8 hz, 2F).

Oligomers. The same oligomers as listed in the acrylonitrile system were present.

α-Methylstyrene System

The neat methylstyrene reactions were carried out with approximately 0.4 ml of olefin. The methylstyrene reactions run in solvent were carried out with approximately 0.4 ml of hexane and 0.2 grams of methylstyrene. An approximate 7 to 1 ratio of methylstyrene to difluoroallene was used in both cases. The reaction mixture composition was determined by quantitative 19F NMR (Figure 43). A delay of 25 seconds was used for all pulse sequences. A minimum of 112 transients was accumulated for all reaction runs.

Endocyclic isomer: 2,2-difluoro-3-methyl-3-phenyl-1-methylenecyclobutane.[5] ^{19}F NMR φ 103.87 (d of m, 1F), 105.07(d of m, 1F).

Exocylic isomer: 3-methyl-3-phenyl-1-(difluoromethylene)cyclobutane.[5] ^{19}F NMR φ 97.01(sept, J=2.6hz, 2 F).

Oligomers. The same oligomers were present as listed in the acrylonitrile system.

Butadiene System

The butadiene reactions were carried out in hexane solvent in an analogous fashion as described for the styrene system. Approximately 0.4 ml of hexane was added to reaction tubes containing hydroquinone inhibitor. Butadiene and difluoroallene were vacuum transferred into the tubes which were then sealed and pressurized. After pressurization was complete the reaction mixture

was analyzed by ^{19}F NMR (Figure 44). A pulse delay of 25 seconds was used. A minimum of 134 transients were obtained.

Endocyclic isomer: 2,2-difluoro-3-vinyl-1-methylenecyclobutane.[4] ^{19}F NMR f 93.20 (dd, J_{FF}=213.2hz, J_{HF}=13.3, 1F), 108.1 (dd, J_{FF}=213.2hz, J_{HF}=7.6hz, 1F).

Exocyclic isomer: 4-(difluoromethylene)-1-cyclohexene.[4] ^{19}F NMR f 95.84 (d, J_{FF}=61.6hz, 1F), 100.09 (d, J_{FF}=61.6hz, 1F).

Compiled Results

The following table (Table 9) is a compilation of various conditions and results from assorted performed high pressure reactions.

Table 9. Conditions and Results from Various Olefins Reacted with Difluoroallene at High Pressures.

Olefin	Pressure (Kbar)	Reaction Time (hr)	Endo+ Exo	% Yield
Styrene	13.0	0.5	2.29	27
	11.03	0.5	2.40	30
	8.03	1.0	3.49	22
	5.99	4.7	4.57	25
	4.10	120	5.29	20
	1.89	142	6.19	24
Methylstyrene	10.87	1.1	1.31	4
	10.40	.9	1.58	2
	7.58	11.0	2.80	-
	5.99	13.78	3.39	11.1
	2.21	109.0	5.00	6.3
Methylstyrene in Hexane	11.03	2.6	2.14	5
	5.99	12.2	3.68	13.6
	2.21	100.5	5.47	11.6
Acrylonitrile	10.87	1.1	2.92	5.5
	5.99	12.2	2.07	8.8
	2.36	37.1	1.36	11.9
Methylacrylo-nitrile	11.03	2.6	2.80	9.4
	5.67	11.0	6.85	10.5
	2.05	124.0	8.55	21
Butadiene	11.03	2.8	11.3*	82.6
	5.99	13.8	29.7*	67.5
	2.21	100.5	55.0*	61.2

The pressures are accurate to ±0.06 Kbar. The reaction times are accurate to ± 0.1hr. The styrene system endo/exo isomer ratios are accurate to better than ± 0.03. All other endo/exo isomer ratios are accurate to ± 0.05. The styrene system yields are accurate to ±5%. All other yields are accurate to ± 0.5%. The Endo+Exo entries (*) for the butadiene system are actually the ratios of [4 +2] cycloaddition product to [2 + 2] cycloaddition product.

APPENDIX A
SELECTED SPECTRA

The figures 105 and 106 represent the spectra for difluoroallene and Z-ß-deuteriostyrene respectfuly. The endo and exocyclic regioisomers from the cycloaddition of Z-ß-deuteriostyrene and difluoroallene, 4-Deuterio-2,2-difluoro-3-phenyl-1-methylenecyclobutane (8) and 2-Deuterio-3-phenyl-1-(difluoromethylene)cyclobutane(9), can be found in figures 107 and 108 respectfully. Representative spectra of the [2 + 2] cycloadditonons of difluoroallne with acrylonitrile, α-methylacrylonitrile, α-methylstyrene, and butadiene can be found sequentially in figures 109 through 112.

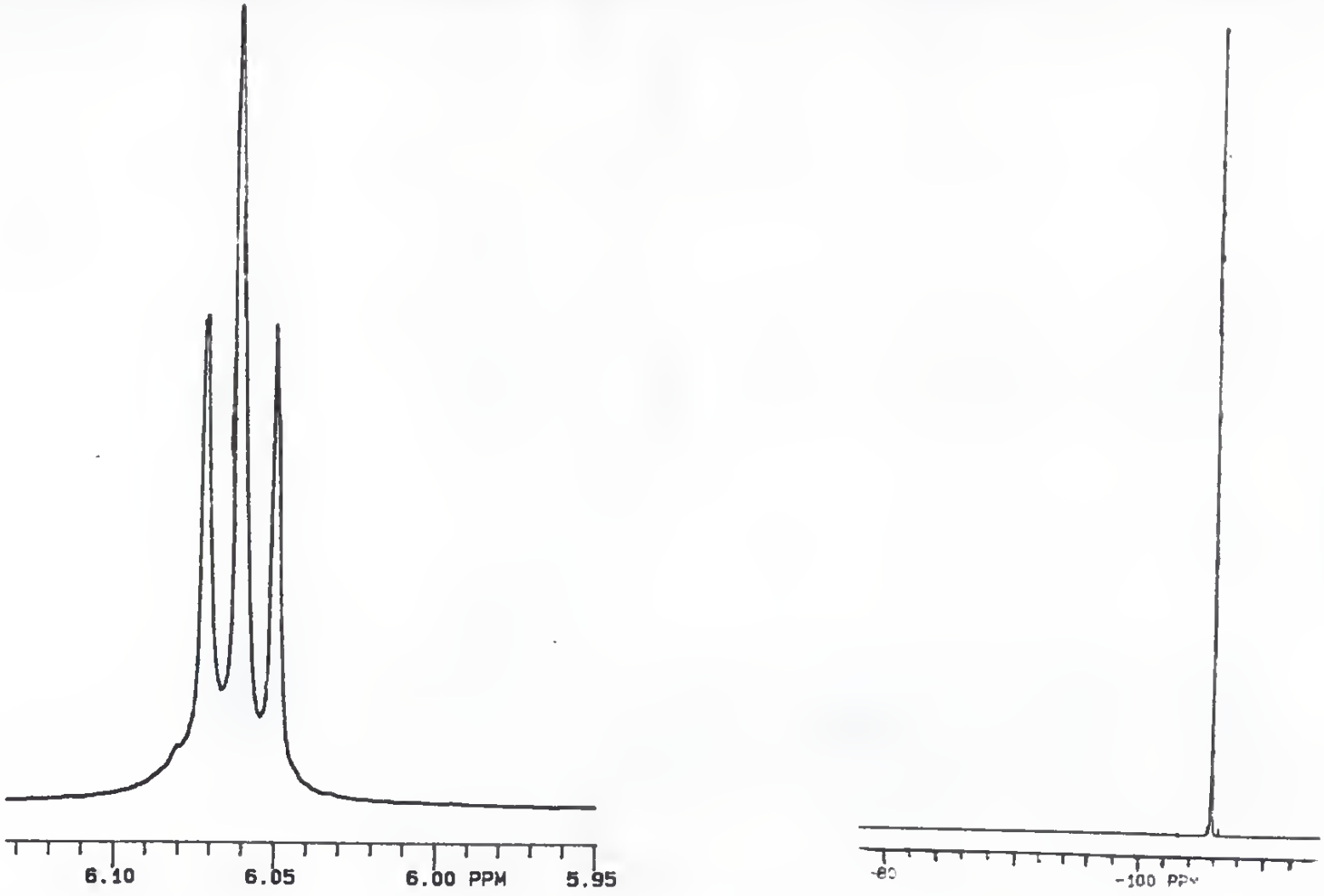


Figure 37. ^{1}H and ^{19}F NMR of Difluoroallene.

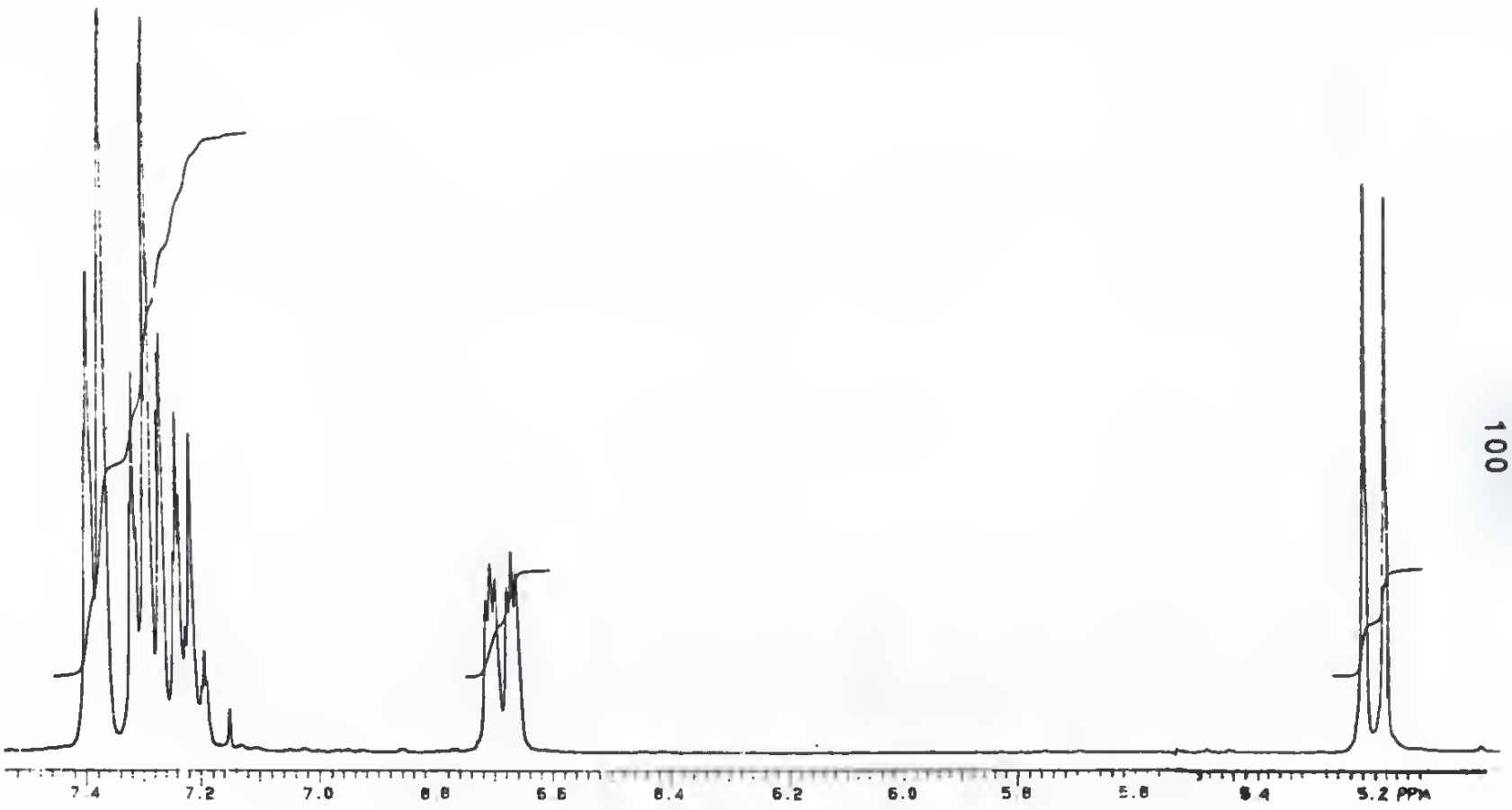


Figure 38. ^{1}H NMR of Z-ß-Deuteriostyrene.

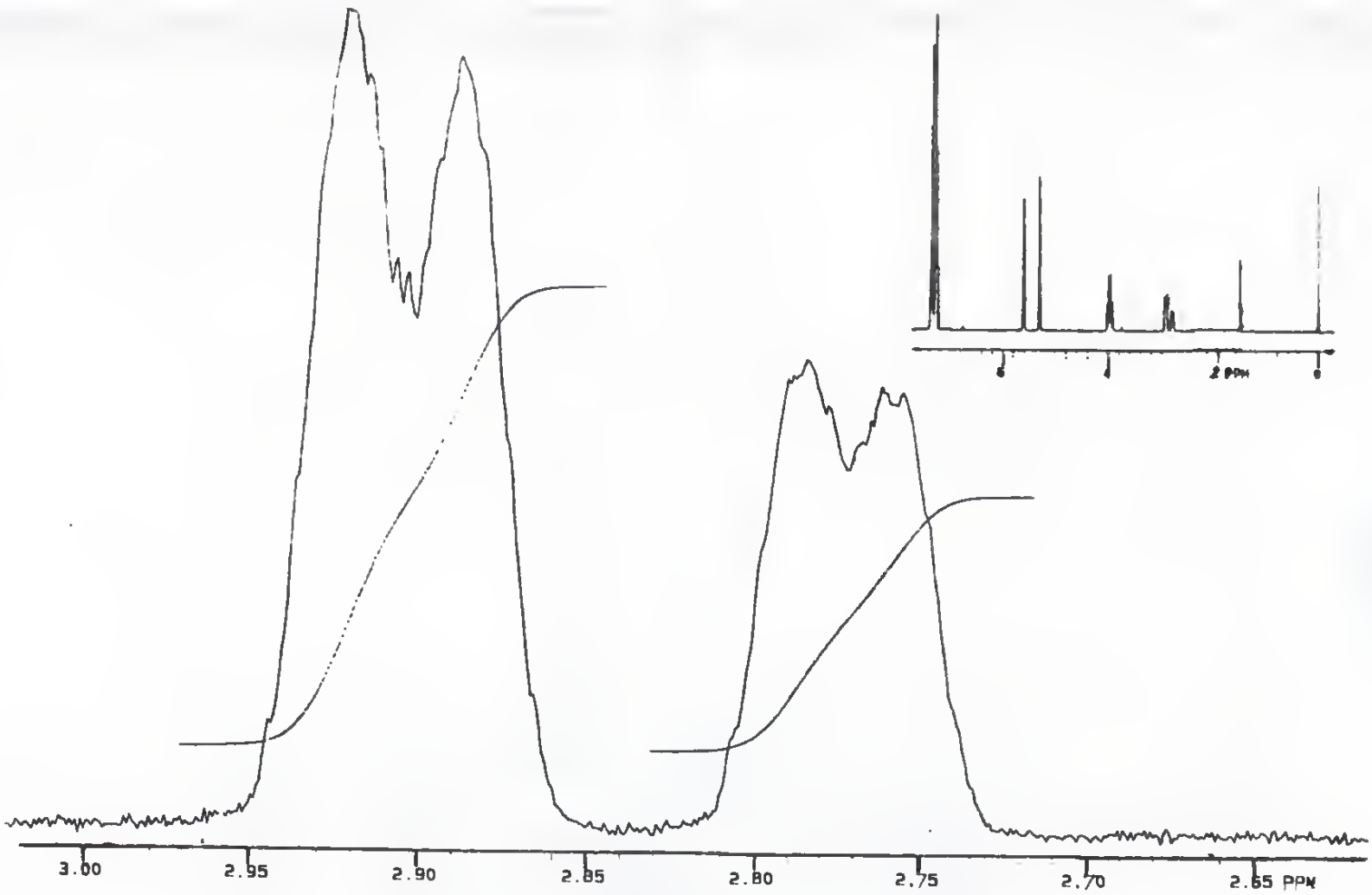


Figure 39. ^{1}H NMR of 4-Deuterio-2,2-difluoro-3-phenyl-1-methylenecyclobutane (8), the endocyclic isomer from the [2 + 2] Cycloaddition of Z-ß-Deuteriostyrene and Difluoroallene.

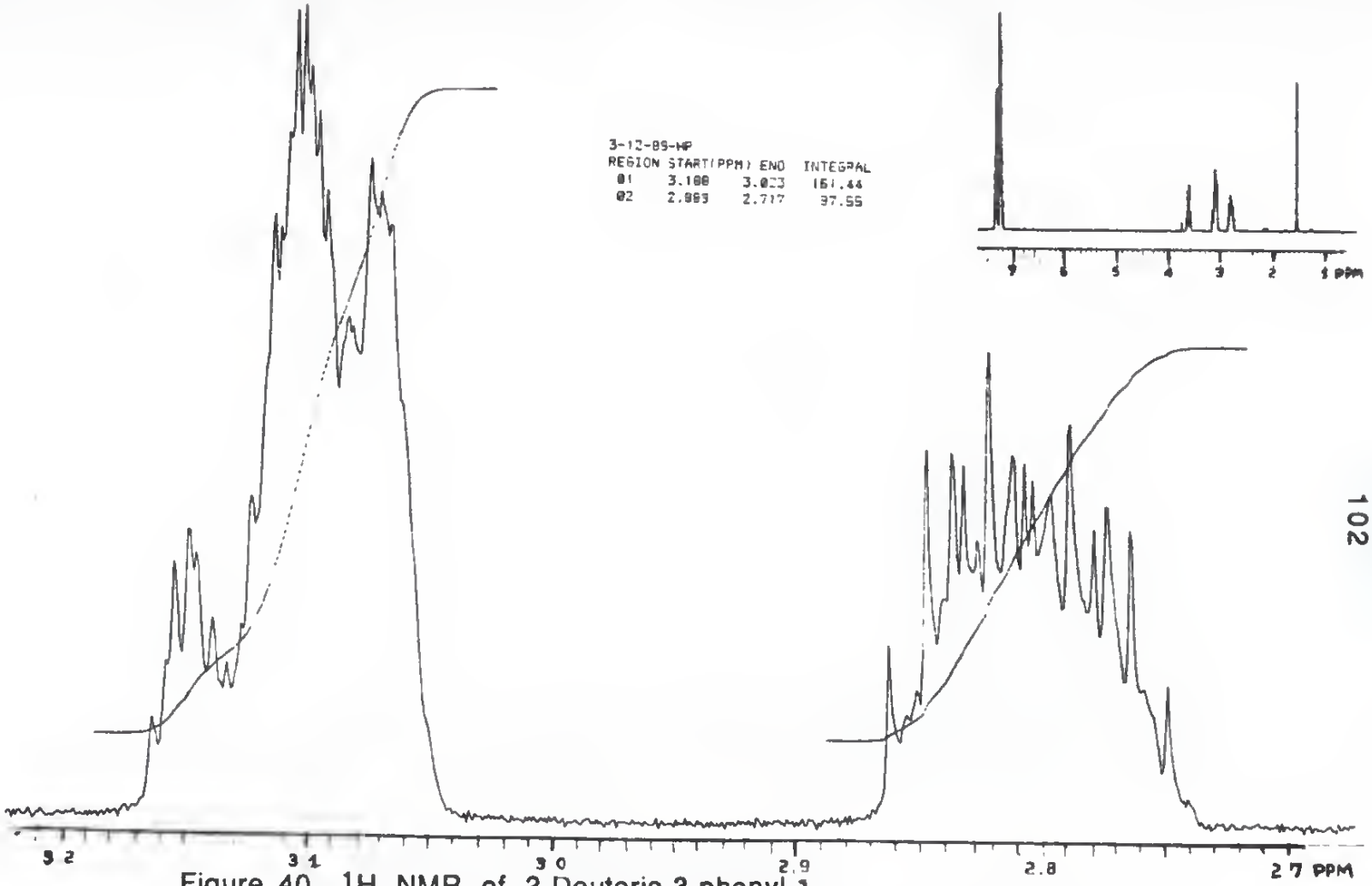


Figure 40. ^{1}H NMR of 2-Deuterio-3-phenyl-1-(difluoromethylene)cyclobutane(9), the exocyclic isomer from the [2 + 2] Cycloaddition of Z-ß-Deuteriostyrene and Difluoroallene.

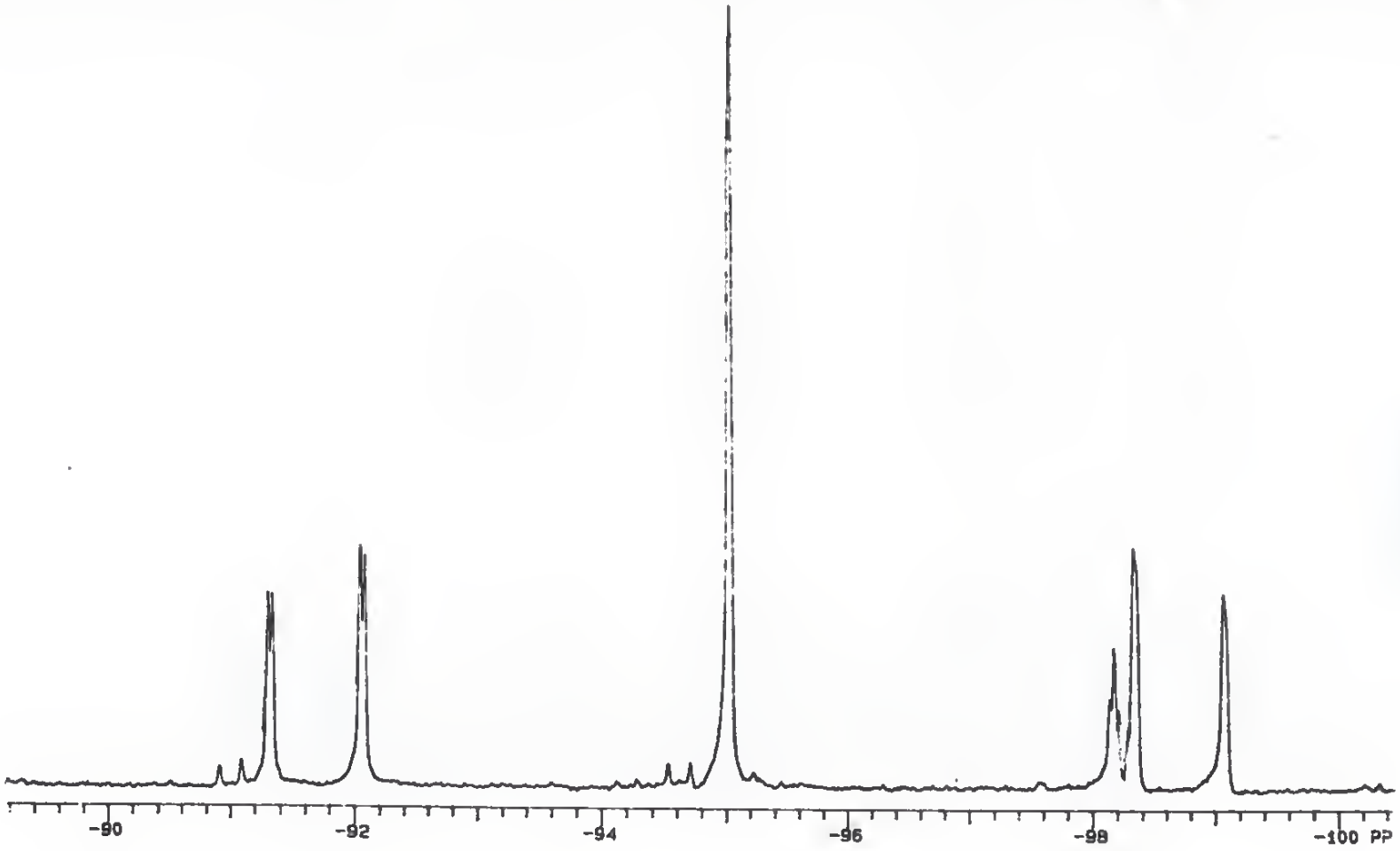


Figure 41. ^{19}F NMR of the Difluoroallene and Acrylonitrile Reaction Mixture.

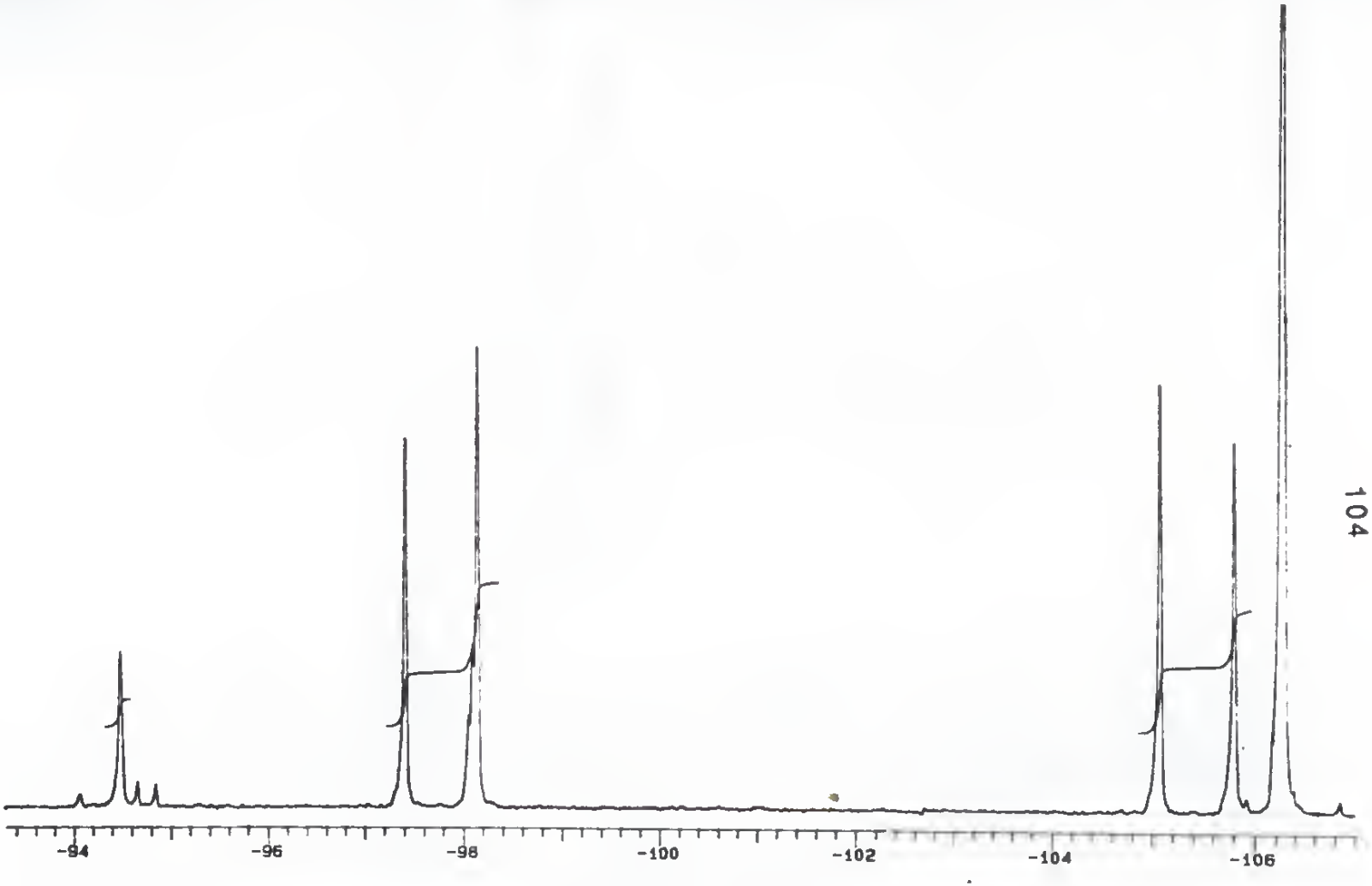


Figure 42. ^{19}F NMR of the Difluoroallene and Methylacrylonitrile Reaction Mixture.

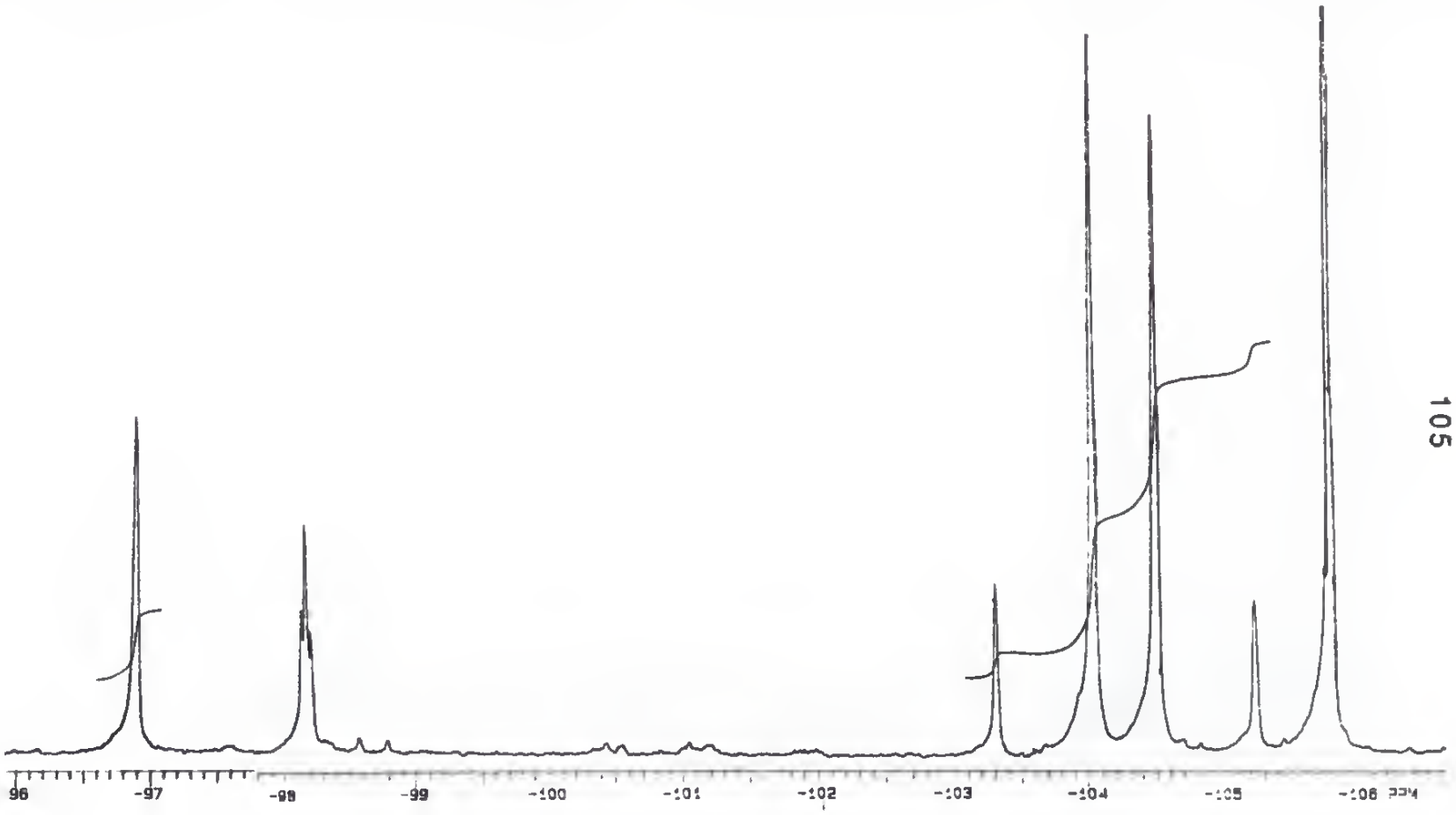


Figure 43. ^{19}F NMR of the Difluoroallene and Methylstyrene Reaction Mixture.

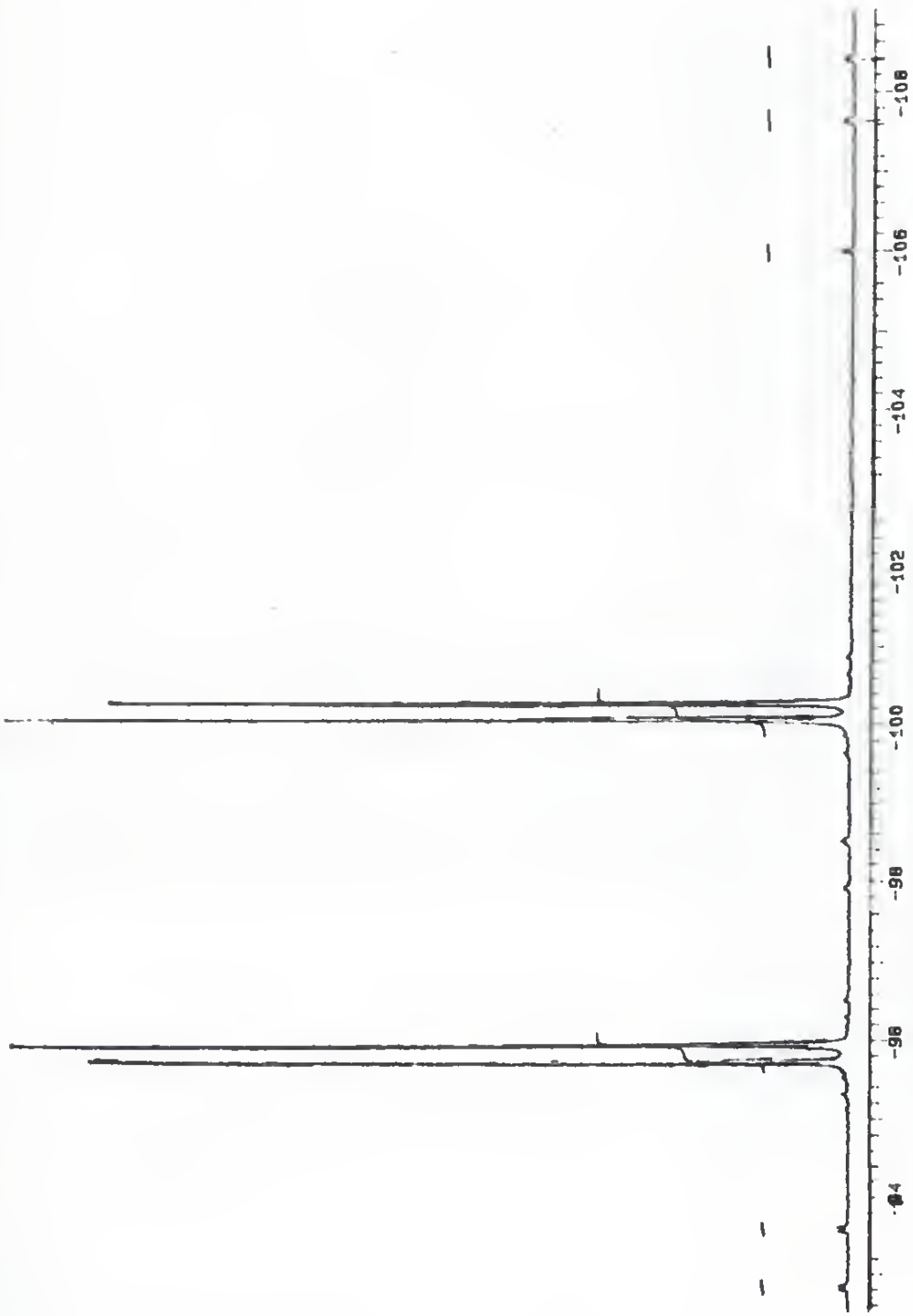


Figure 44. ^{19}F NMR of the Difluoroallene and Butadiene Reaction Mixture.

APPENDIX B
THE HIGH PRESSURE APPARATUS

All high pressure experiments were carried out using the same double walled simple piston-cyclinder type high pressure reaction apparatus. The apparatus consists of a heavy duty steel press frame which surrounds and gives support to the press itself. The pressure force is supplied by an electric hydraulic pump (Enerpac, 1321 series). This pump pressurizes hydraulic fluid which is used to extend the hydraulic ram (100 ton capacity). The hydraulic ram is mounted on the lower plate of the press frame, as the ram is extended, it comes in contact with, and lifts the reaction cylinder. The reaction cylinder contains a cylindric bore through it's center, the top and bottom of which is sealed by pistons and Bridgeman seals. The top piston is butted against and supported by, via a series of spacer blocks, the upper plate of the press frame. As the reaction cylinder is raised, the top piston is forced into the reactor bore. The displacement of the piston into the reactor bore, increases the pressure within the cavity, and by means of a non-compressible pressure conducting fluid (kerosene) filling the reactor bore, the pressure is exerted on the reaction sample tubes and the pressure within the tubes is increased.

The internal reactor pressure is monitored by the deflection of an in-line gauge. The pressure within the reactor bore is simply the force, applied to the cylinder and observed on the in-line gauge,

multiplied by a force amplification constant. This force amplification is brought about by the unequal ram and piston areas. The pressure within the reactor bore is equal to the in-line gauge pressure multiplied by the ratio of these areas (ram area ÷ piston area) or 45.7.

The reaction cylinder itself consists of a hardened (Rc 45) S-5 tool steel cylinder into which has been press fit a hardened (Rc 54) Vascomax 300 steel liner. This liner has been subjected to an ultrasonic and magnetic flux test to verify it being free of cracks, voids, and impurities. The cylinder liner has a 0.757" diameter bore drilled through the center. This center bore is the reaction cavity. The bore is filled with the reaction containers and a pressure transfer fluid and sealed at top and bottom by pistons and Bridgeman seals. The pistons are made of hardened (Rc 45) S-5 and are precisioned machined to match the bore diameter. The Bridgeman seals consist of a series of bronze delta rings, neoprene O-rings, and teflon O-rings.

None of the common high pressure reaction containers; clamped teflon tubes, syringes, and bellowed copper tubes, were adequate for our purposes. It was necessary to have a reaction cylinder into which gases could be condensed, hence the material must be able to withstand liquid nitrogen temperatures and they must also be able to be air-tight sealed. In addition the vessels must be quite malleable in order for the pressure within the reactor bore to be adequately conducted to the contents within the sample tubes. A thin-walled (0.04") low density polyethylene tubing was found to

be suitable for our purposes. This tubing is able to be purchased from AIN Plastics of Mount Vernon, NY. It is able to withstand liquid nitrogen temperatures without cracking upon warming, it can be securely sealed with a cool flame in a manner similar to glass, and polyethylene is quite malleable. Schematics of all high pressure equipment can found at the end of this appendix.

A Typical High Pressure Reaction

A low density polyethylene tube of approximately 15 cm in length is heated at one end with a cool flame. As the material turns transparent the end is pressed flat and reheated to ensure an intact bond forms between the tube walls. The tube is then allowed to cool and hydroquinone is added along with any desired liquid solvent or starting material. The bottom sealed end of the tube is cooled to approximately -78° C (this temperature is dependent on the flammability of the tube contents) to prevent ignition of the solvent or starting material as the upper end of the tube is now flame heated until just transparent, and then slid onto a tapered glass tube fitted with a 10/20 joint. The material about the polyethylene-glass juncture is then reheated to ensure a reliable seal with the glass. The sample tube having been fit with a glass joint can then be connected to a vacuum line. All gaseous reactants are transferred into the sample tube using standard vacuum line techniques. A single degassing of reactor contents is recommended as more degasings have a tendency to impair the integrity of the tube. The sample tube is sealed in a manner analogous to sealing a glass reaction tube,

with the exception that a much cooler flame is utilized. The sealed reaction tube is placed in the reaction cylinder bore, kerosene is added until the level is approximately 1 cm below the cylinder rim. The piston head is inserted and seated into the bore. The piston head is followed by a bronze delta ring, a neoprene O-ring, a teflon O-ring, two more delta rings and the piston body. The cylinder is centered over the hydraulic ram and the top piston is topped with the appropriate amount of spacer blocks to minimize the distance to the top of the press frame. The line check valve is closed and the ram is extended by the hydraulic pump until the spacer blocks become pressed snug against the press frame. The pump is turned off and an accurate 90° alignment between the piston and the top of the reaction cylinder is made. The proper alignment is critical for safe and prolonged operation of the high pressure apparatus. The safety door is screwed shut and the pump engaged until the desired line gauge reading is achieved. It is frequently necessary to bump up the pressure periodically within the first half hour of pressurization. This is due to the dissipating of heat which was generated upon pressurization. Upon completion of the reaction, the pump is turned on and the line check valve is opened. The pistons, seals, and reaction containers can be removed once the reaction cylinder has descended onto the center press frame support. The reaction mixture can then be analyzed or purified by appropriate means.

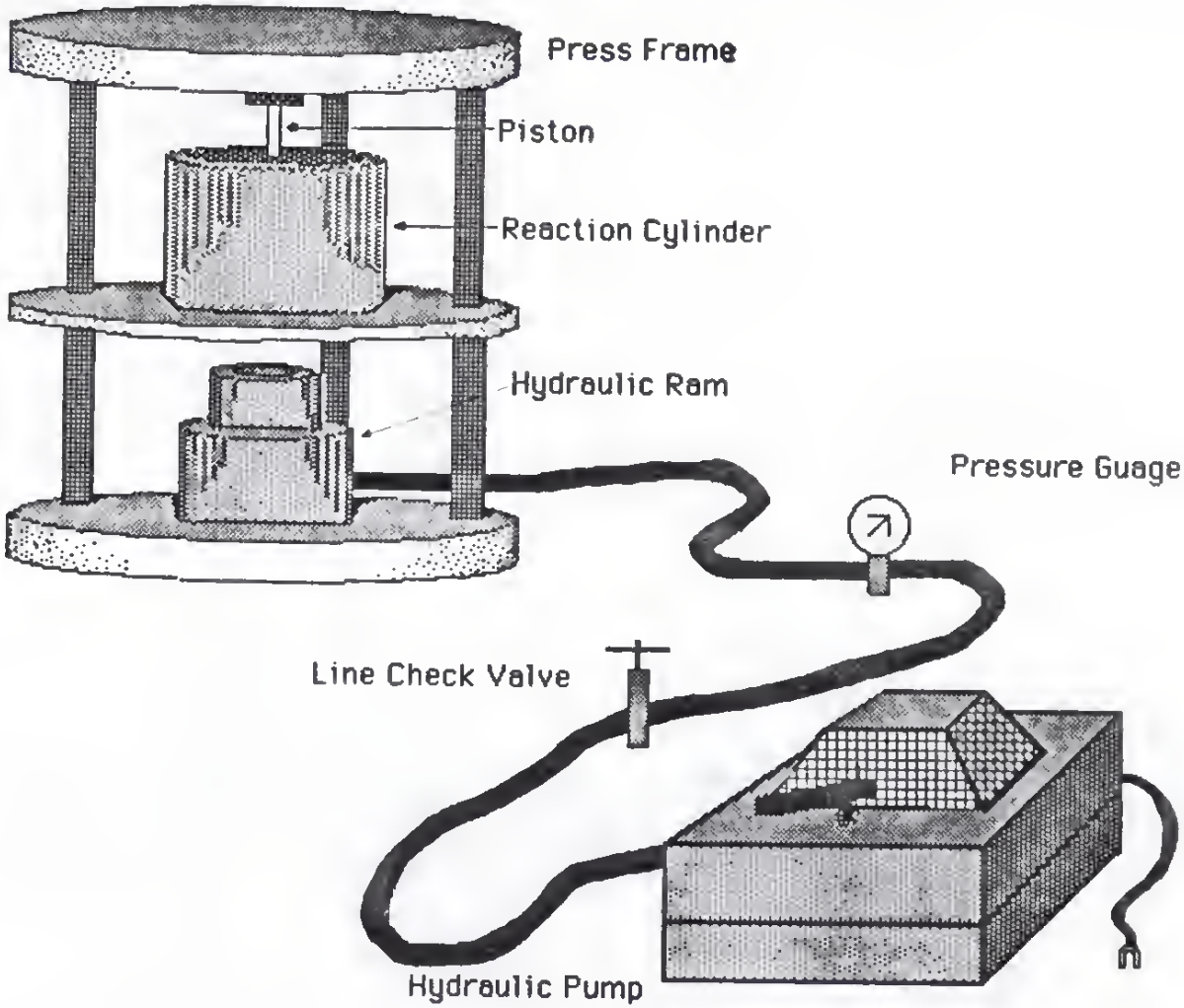


Figure 45. Schematic of the High Pressure Reaction Apparatus.

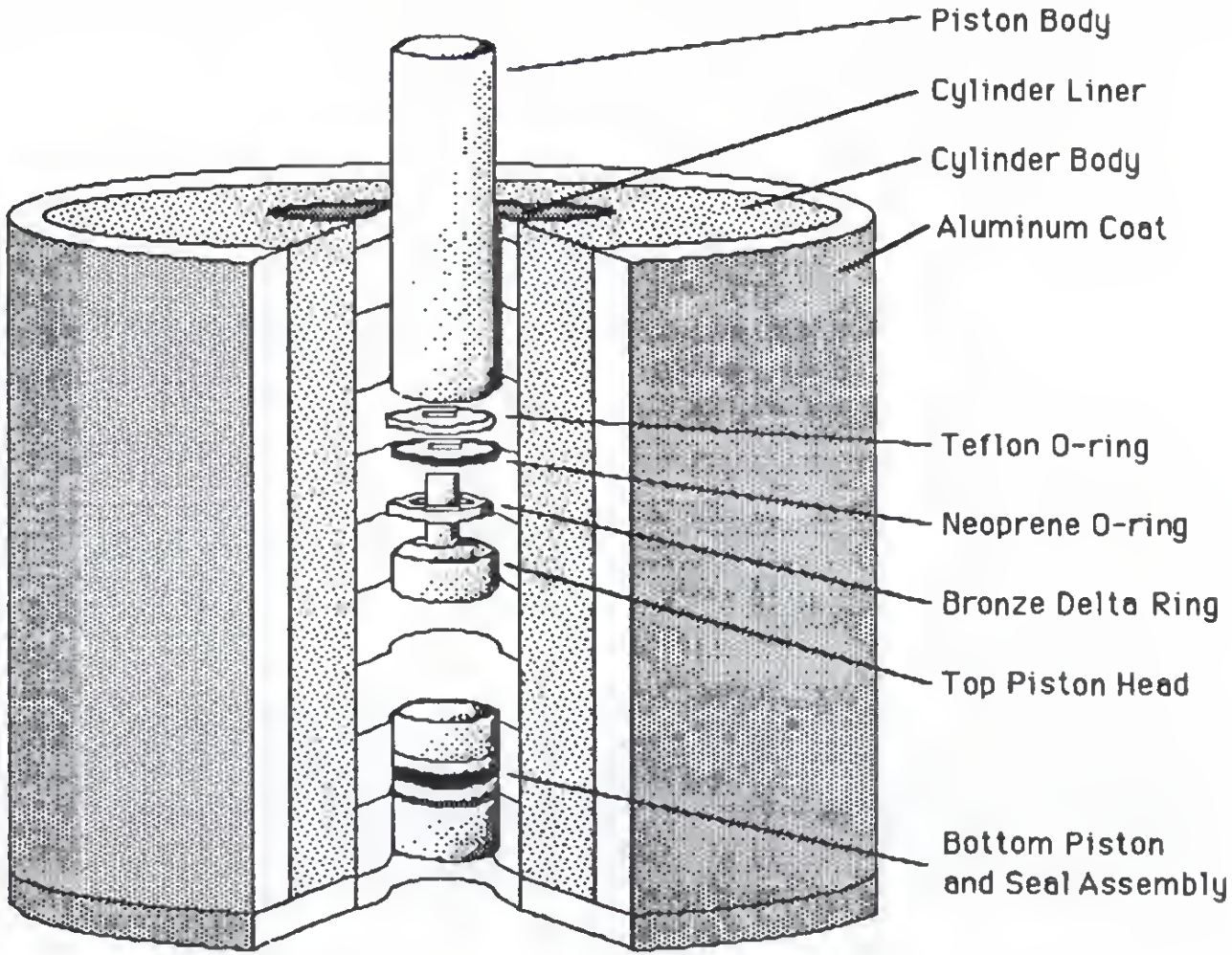


Figure 46. Cross Section of the High Pressure Reaction Cylinder.

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BIOGRAPHICAL SKETCH

Sarah L. Weaver was born on December 16, 1962. Due to the fact that her father was in school at the time, the location was none other than Gainesville, Florida. She was raised in the sleepy town of Inverness, Florida, where she was a member of F.F.A. (Future Farmers of America) and 4-H. Her principal concerns while growing up were for her horse and pigs. Thanks to inspiring teachers and supportive family she ventured to the "big city" to begin her quest for higher knowledge.

Sarah returned to Gainesville in 1982 and received her B.S. in chemistry from the University of Florida in May of 1985. After toying with the idea of medical school, and realizing her heart belonged to chemistry, she began her graduate career in August of 1985.

The insanity which ubiquitously accompanies an extended stint in graduate school was successfully (?) warded off with a reasonable smattering of extracurricular activities. These include racquetball, weight training, scuba diving, bicycling, and more recently, roller blading. She hopes to recover a solid grasp on her sanity upon earning her Ph.D. in August 1990.

Upon completion of her final graduate requirements, she is (finally) moving far away from Gainesville. Sarah has accepted a position with Shell Development Corporation. She is eagerly awaiting the commencement of her career, the fresh challenges to be met, and the excitement of living in Houston.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

William R. Dolbier, Jr.
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

William M. Jones
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

John A. Zoltewicz
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Robert J. Hanrahan
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

William R. Kem
Professor of Pharmacology
and Therapeutics

This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

August 1990

Dean, Graduate School

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